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SPECIAL ISSUE ON ACTH AND CORTISONE


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535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

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We feel that case hardened lenses should be used more widely for general wear especially for children and for grown-ups who go in for sports, handball for example, where a splintered lens could result in serious injury.

It may be interesting to see what goes into the making of hardened lenses. To start with the lens to be treated must be at least 2.8 mm. at its thinnest point. 3.0 mm. or 3.4 mm. minimum thickness is better because a more resistant lens results.

The lens is placed in a furnace and heated almost to the softening point. This point is critical and must be controlled exactly because if heated above the softening point, it would sag and distort; if heated below its strain point, no marked increase in impact resistance would result.

When the lens is at exact temperature a cold air blast is turned on both sides of the lens simultaneously. The cold air blast contracts the glass on the surface and sets up stresses on the surface which are relieved in the core. The result is a high state of compression on the surface of the glass.

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As pointed out earlier, it is necessary for a lens to be at least 2.8 mm. thick at its thinnest point. This minimum thickness gives the necessary volume to incorporate the stresses. So it becomes evident that case hardened lenses will be much too heavy for high minus or plus corrections.

If these high plus or minus cases must have a safety lens it is better to prescribe a laminated glass. For most corrections, however, the case hardened lens works very well and in the case of the active child is almost a necessity.

"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

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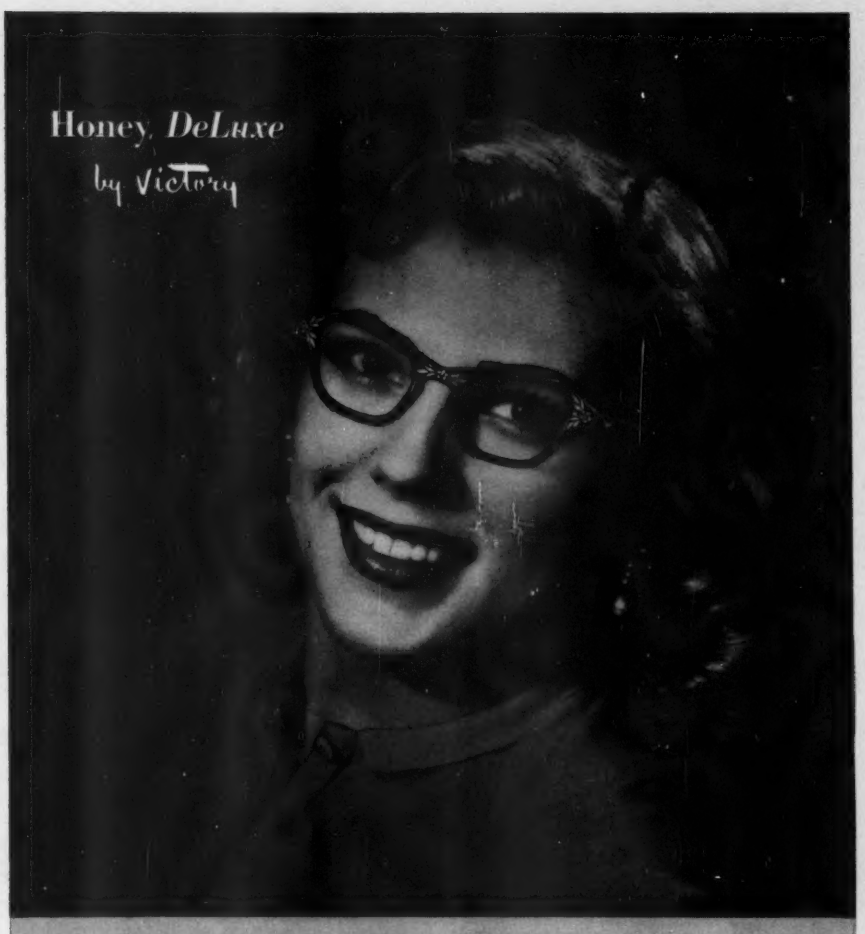


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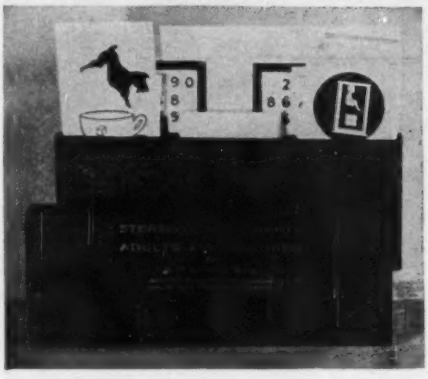

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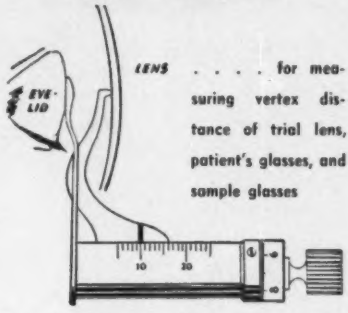


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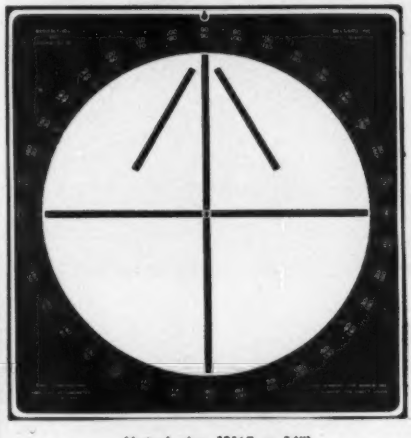

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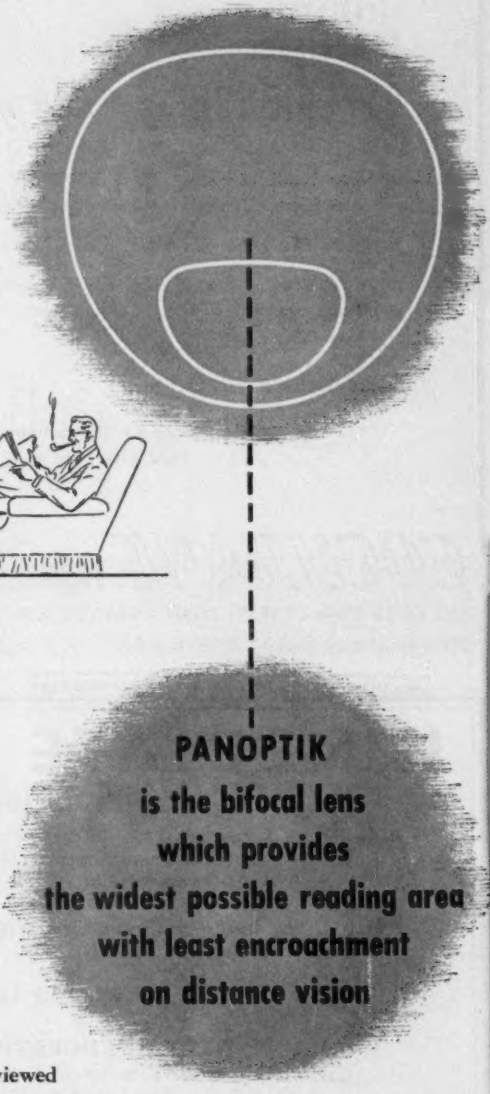


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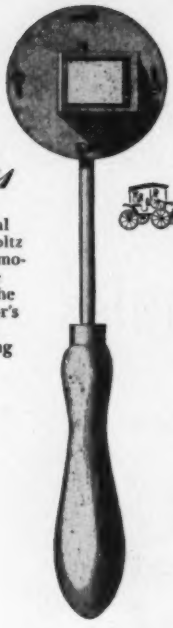

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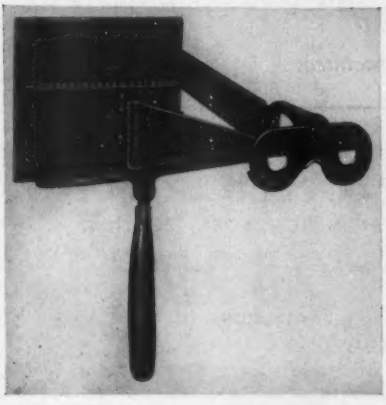

Horizontal and vertical deviations and cyclophoria may be measured on the chart of this instrument. The red arrow points to a vertical row of red figures and indicates the degree of hyperphoria. The white arrow points to a row of horizontal figures and indicates es- or exophoria. Cyclophoria is denoted when the red arrow does not appear parallel to the horizontal white line and its degree is recorded on the small scale at the right of the chart. The working distance is 33 cms and the horizontal and vertical deviations are recorded in prism diopters.

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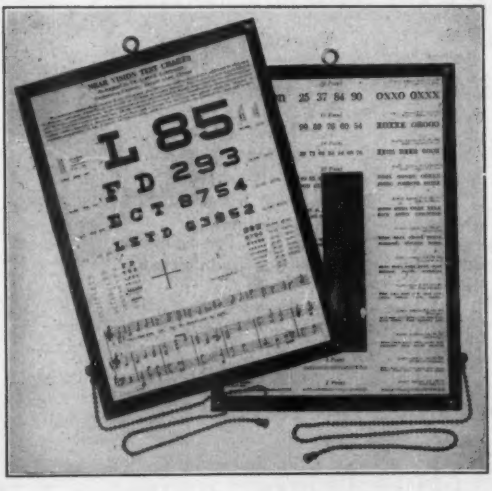


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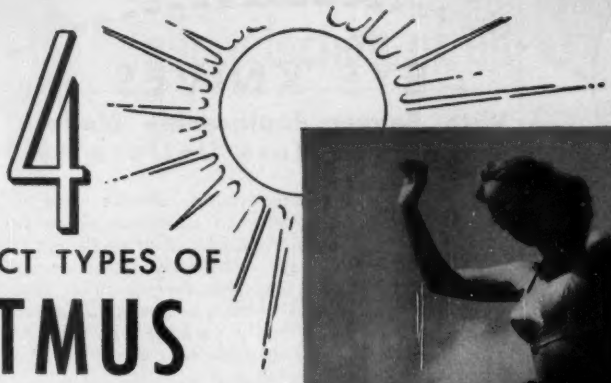

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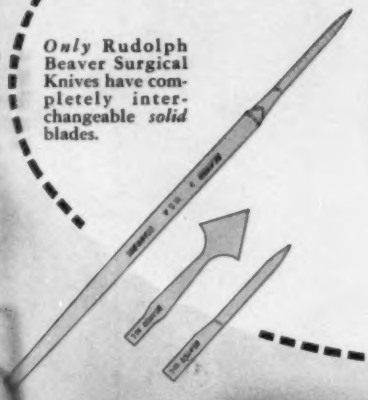

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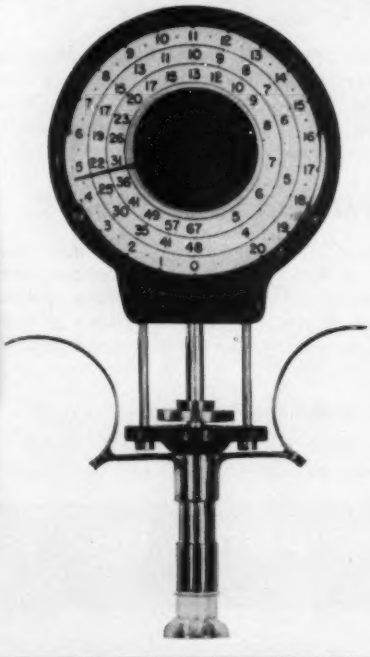

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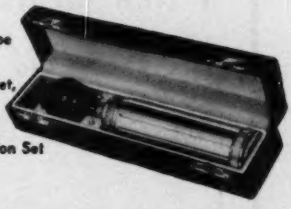

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# OCULAR MANIFESTATIONS OF DIFFUSE COLLAGEN DISEASE

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CHICAGO

THIS review was first stimulated by the observation that many ocular syndromes of obscure origin involved the cornea and sclera, tissues rich in connective tissue elements. Also, the association of scleritis, episcleritis, tenonitis and iritis with the "rheumatic" diathesis had been described in the clinical literature and pointed to a common denominator which might explain the ocular and articular findings. Klemperer and his group had proposed that the connective tissues throughout the body acted as an organ which was afflicted in a number of diseases, which they called "collagen diseases." It was in these conditions that the early work with the pituitary adrenocorticotropic hormone (ACTH) and cortisone (11-dehydro-17-hydroxy-corticosterone) produced the most dramatic results. Therefore, it seemed that a review of the development of the concept of collagen disease not only might lead to a better understanding of certain ocular conditions but also might provide a more rational basis for future ACTH and cortisone therapy in diseases of the eye.

Much of the earlier thought in clinical medicine and pathology stemmed from Morgagni's idea that a given disease resided in a specific organ. This simple thesis failed to explain many of the observed facts. Gradually, the correlation of clinical and laboratory observations with necropsy findings led to the awareness of an interdependence of certain organs and tissues to form organ or tissue systems. Even the knowledge that the hemopoietic and reticuloendothelial systems existed did not provide an essential site in every disease, since a number of acute infections and "intoxications" did not produce characteristic, or even significant, lesions in any organ or system. Futhermore, the involvement of apparently unrelated organs in such diseases as rheumatic fever and rheumatoid arthritis pointed up the need for a broader conception of morbid processes than had been formulated.

It was Klinge [1] who first proposed that the characteristic organ and tissue changes in these diseases was secondary to diffuse involvement of the connective tissues of the body. He described the fibrinoid alteration of the collagenous tissue and the myxomatous swelling of the ground substance. Klinge believed that tissue damage in human rheumatic disease was due to hypersensitivity, since he and Gerlach [2] had demonstrated similar connective tissue changes in rabbits rendered

This study was aided in part by a fellowship grant from the Heed Ophthalmic Foundation.

From the Department of Ophthalmology of the University of Illinois College of Medicine and the Illinois Eye and Ear Infirmary.

1. Klinge, F.: Der Rheumatismus, Ergebn. d. allg. Path. u. path. Anat. **27**:1, 1933.

2. Gerlach, W.: Studien über hyperergische Entzündung, Virchows Arch. f. path. Anat. **247**:294, 1923.

hypersensitive to foreign proteins. Jäger [3] and Rössle [4] lent credence to this hypothesis when they independently proposed that fibrinoid degeneration of collagen was a constant and characteristic feature of allergic disease. They classified rheumatic fever, essential polyangiitis and thromboangiitis obliterans in a single group because these entities are characterized anatomically by fibrinoid changes in the connective tissues. The group of observers who associated fibrinoid alteration of collagen with the hypersensitivity response was augmented by Masugi and Yä,[5] who noted fibrinoid vascular lesions in scleroderma. Klemperer, Pollack and Baehr [6] (1941) elucidated the pathology of acute disseminated lumps erythematosus and considered the possibility that the widespread collagenous injury might have had an allergic background. Rich [7] reported a serum sickness type of protracted anaphylactic hypersensitivity reaction in a series of seven patients exposed to foreign serum and sulfonamide therapy. Muscle biopsies in these cases showed microscopic changes compatible with the diagnosis of essential polyangiitis.

Klemperer, Pollack and Baehr [8] cautioned that although hyperergic inflammation is characterized by fibrinoid degeneration of collagen, it does not necessarily follow that widespread fibrinoid degeneration indicates an allergic basis. Klemperer [9] explained that other bits of evidence led his group to suspect that fibrinoid collagen change need not indicate an allergic origin. He cited Askanazy's demonstration of local fibrinoid alteration in the base of peptic ulcers and in the vicinity of pancreatic necrosis. These were situations in which the mechanism of hypersensitivity could be excluded, he concluded. Another point was scored against the exclusive role of hypersensitivity when Wu [10] induced fibrinoid collagen alteration in the skin of the rat secondary to slight mechanical trauma. Harkavy, discussing Criep and Mayer's [11] paper on experimental collagen disease, stated that fibrinoid collagen change can be induced by direct action of toxins or by means of enzymes, such as hyaluronidase or collagenases, present in some bacterial toxins. He also drew attention to Robinson's demonstration of collagenous degeneration secondary to dietary deficiencies. Hypersensitivity was definitely excluded as a pathogenetic factor in the experimental hypertension which produced vascular

3. Jäger, E.: Zur pathologischen Anatomie der Thrombangiitis obliterans bei juveniler Extremitätengangrän, Virchows Arch. f. path. Anat. **284**:526, 1932.

4. Rössle, R.: Zum Formenkreis der rheumatischen Gewebsveränderungen, mit besonderer Berücksichtigung der Rheumatischen Gefässentzündungen, Virchows Arch. f. path. Anat. **288**: 780, 1933; Klin. Wchnschr. **15**:809, 1936.

5. Masugi, M., and Yä, S.: Die diffuse Sklerodermie und ihre Gefässveränderung, Virchows Arch. f. path. Anat. **302**:39, 1938.

6. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941.

7. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by 7 Cases Developing During Serum Sickness and Sulphonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123, 1942.

8. Klemperer, P.; Pollack, A., and Baehr, G.: Diffuse Collagen Disease: Acute Disseminating Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **119**:331 (May 23) 1942.

9. Klemperer, P.: The Concept of Collagen Diseases, Am. J. Path. **26**:505, 1950.

10. Wu, T. T.: Über Fibrinoidbildung der Haut nach unspezifischer Gewebsschädigung bei der Ratte, Virchows Arch. f. path. Anat. **300**:373, 1937.

11. Criep, L. H., and Mayer, L. D.: Experimental Collagen Disease from Hypersensitization to Streptococcus Toxin, J. Allergy **20**:243-254, 1949.

necrosis simulating polyarteritis. This was shown independently by Byrom and Dodson, Winternitz and associates, Holman, Duff and associates, and Koletsky, as cited by Klemperer.[9] Klemperer inferred from this that "an apparent similarity in the histologic picture does not denote identity of tissue lesions and certainly not unity of process and pathogenesis."

Klemperer and his followers were convinced that, whatever the etiology, a common denominator existed in the modifications of the extracellular portions of the connective tissue, and he indicted the connective tissue as an organ which was the common seat of a number of heterogeneous diseases. They coined the term "collagen disease" to describe a group of obscure and diverse maladies that shared certain structural changes, with no intent to imply diagnostic or pathogenetic significance. The acute and chronic diseases that most frequently have been included in this group are rheumatic fever, rheumatoid arthritis, essential polyangiitis (the newer terminology for "periarteritis nodosa"), acute disseminated lupus erythematosus, scleroderma and dermatomyositis.

## THE CONNECTIVE TISSUE

*Morphology.*—In order to justify the proposition that these diseases, with protean manifestations, were in the nature of a systemic disease of the connective tissue, Klemperer and his associates[8] felt it necessary to demonstrate first the existence of a connective tissue system. A system, in the biologic sense, they defined as an assemblage of organic structures composed of similar elements combined for the same general function. They believed that the connective tissue fulfilled these requirements, since it consists of an association of similar cellular and fibrillar elements held together by a third substance, an amorphous ground, or cement, substance. The cellular elements are chiefly fibroblasts; the fibrillar elements are made up of collagen, reticulin and elastin.

*Physiology.*—The connective tissues function chiefly for binding and support. The Klemperer school stated that the connective tissue is interposed between parenchymal cells and the blood and lymph spaces and hence serves to transfer metabolites and to regulate salt and water balance. Duff[12] did not agree that the connective tissue system has anything to do with general body economy in an active way. He believed that connective tissue serves as support in a passive way and that it cannot aid in the regulation of salt and water balance.

The ground substance has been the subject of much investigation in recent years, and the answer to the riddle of collagen disease may come from better understanding of the nature of this interfibrillary substance. Its origin is still in doubt. Schade[13] stressed the colloidal nature of the ground substance. Meyer, cited by Duran-Reynals and Goldsmith,[14] established the mucopolysaccharide nature of hyaluronic acid, the component of the ground substance which is the substrate on which "spreading factors," such as hyaluronidase and other mucolytic enzymes, act. Duran-Reynals and Goldsmith[14] reported that fluctuations in the permeability

12. Duff, G. L.: Diffuse Collagen Diseases: Morphological Correlation, Canad. M. A. J. **58**:317, 1948.

13. Schade, H.: Die physikalische Chemie der inneren Medizin, Dresden and Leipzig, Theodor Steinkopff, 1923.

14. Duran-Reynals, F., and Goldsmith, E. D.: Ground Substance of the Mesenchyme and Hyaluronidase: A Symposium, Science **110**:74, 1949.

of the ground substance occur as a result of contact with mucolytic enzymes, alterations in the hydration and from the effects of estrogenic, gonadotropic and adrenocortical hormones. Infection, they pointed out, is closely conditioned by a variety of physiological factors which find a direct expression in the permeability of the ground substance. Fluctuations in this permeability result in corresponding fluctuations in the severity of the infectious process.

*Chemistry.*—The mucopolysaccharide nature of hyaluronic acid has been noted. Of the fibrillar elements, most of the attention has been centered on collagen, which is the principal solid constituent of white fibrous tissue. Collagen is classified as a simple protein, which by definition is one which yields alpha-amino acids and their derivatives on hydrolysis. Simple proteins are further subdivided into albumins, globulins, albuminoids, etc., on the basis of solubility and other characteristic properties. The collagens, along with the elastins and keratins, are albuminoids. These are fibrous proteins which have a supporting or protective function in the animal organism. The composition of the collagen molecule, within the framework of accepted chemical differences, is as follows: Aminoacetic acid (glycine) represents one third of all the amino acid residues in the molecule; proline and hydroxyproline, one third, and other amino acids, one third. Collagens are digested slowly by pepsin hydrochloride but are resistant to tryptic digestion. They are converted into easily digested soluble proteins, the gelatins, by boiling with water, dilute acids or alkalis.[15]

One of the factors which complicates the study of collagen disease is the fact that the collagens from various sources in the animal organism differ in their chemical composition. Therefore, connective tissues bearing great resemblance to each other morphologically may be quite different in their chemical nature and response to various stimuli.[15]

*Response to Trauma.*—The nature of the pathological changes in diffuse collagen diseases may be appreciated more fully by reviewing the type of connective tissue response to injury. The nature of the trauma, i.e., physical, bacterial or allergic, may determine whether the tissue reaction is proliferative or degenerative. Some insults evoke a proliferative response that consists of increased cellular production. In other reactions alterations in the fibrillar elements and ground substance predominate. Keloid formation after connective tissue injury results from excess production of collagenous fibers and ground substance.

In dealing with these diseases, most writers have used the descriptive term "fibrinoid degeneration" to indicate certain well defined optical and staining alterations in collagenous fibers and the ground substance as they appear with the routine histological technics. The fibers become straightened and thickened; the refractivity of the bundles is increased, and the appearance of apparent friability is created. Tissue eosinophilia of varying degrees develops, and there is an increase in the ground substance. Klemperer concluded that these changes can be due only to a profound physicochemical aberration of the colloid state of the connective tissues. He cited MacCallum to the effect that such a derangement is always present but that the routine technics fail to reveal it. All the diseases listed above show fibrinoid degeneration in histological sections. Scleroderma has, in addition,

15. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, Philadelphia, The Blakiston Company, 1948, p. 217.

an increase in the bulk and density of the connective tissues. This type of sclerosing change is also noted occasionally in the spleen and pericardium in cases of acute disseminated lupus erythematosus. The case to case variation in demonstrable changes is great. Clinical reversibility of these conditions suggests a transient colloidal imbalance.

Marked differences exist in the evolution of the characteristic lesions in collagen diseases. The vascular lesions of lupus erythematosus and essential polyangiitis are more striking than those of rheumatic fever. On the other hand, the specific granulomatous Aschoff nodule of rheumatic fever never occurs in the other diseases. The connective tissue system is altered in all diseases of this group, but the etiological agents and the nature of the alteration may be dissimilar. Yardumian and Kleinerman [16] believed that the degenerative changes noted in the collagenous tissue in so-called diffuse vascular or collagenous disease represent a secondary phenomenon. The tissues primarily affected are the small arterioles and capillaries. The resultant chronic anoxemia produces the degeneration in the surrounding collagenous tissue. They believed that the terms "fibrinoid degeneration" and "collagenous disease" are descriptive only with respect to the end result of the pathological process.

## OCULAR MANIFESTATIONS

It is beyond the scope of this discussion to present the detailed clinicopathological picture of all diseases that alter human connective tissues. Essential polyangiitis, acute disseminated lupus erythematosus, rheumatoid arthritis, scleroderma and dermatomyositis may present ocular manifestations. There are, in addition to these recognized systemic disorders, a number of purely ocular diseases of obscure origin that may be local manifestations of collagenous system imbalance. I shall review the ocular findings associated with the systemic diseases and then attempt to show the possible implications of the collagen system in some heretofore unsolved ophthalmological problems.

Although the ocular lesions previously reported are presented, no attempt has been made to give a detailed account of all series or case reports of these diseases in the literature.

*Acute Disseminated Lupus Erythematosus.*—The general pathological picture is not always diagnostic, but the following changes occur: (1) capillary dilatation with extravasation of blood and serum; (2) proliferative endothelial lesions with thrombus formation (not described in the retinal vessels), and (3) degenerative or necrotizing lesions in the walls of capillaries, arterioles and venules, often with hemorrhage into adjacent tissues. Hyaline capillary thrombi are said to be widespread and characteristic, along with nonbacterial endocarditis and "wire loop" lesions in the kidneys.

Maumenee [17] reported a series of four cases of acute disseminated lupus erythematosus and one case of chronic disseminated lupus erythematosus, the latter terminating in fulminating tuberculosis. The diagnosis was made on the clinical findings and was substantiated by pathological studies. The essential

16. Yardumian, K., and Kleinerman, J.: Pathogenesis of So-Called Diffuse Vascular or Collagen Disease, Arch. Int. Med. **83**:1 (Jan.) 1949.

17. Maumenee, A. E.: Retinal Lesions in Lupus Erythematosus, Am. J. Ophth. **23**:971, 1940.

ophthalmoscopic findings (not present in all cases) were (1) slight edema of the nerve head, (2) superficial retinal hemorrhages, and (3) grayish to white patches of "exudate," usually near the posterior pole. Histopathological study revealed that the areas of so-called exudate corresponded to areas of cytoid bodies in the nerve fiber layer. The cytoid body is an oval, homogeneous, mildly acidophilic structure. These areas of "exudate" varied in thickness from a few cells to patches twice the thickness of the nerve fiber layer. None of the sites of the cytoid bodies touched retinal vessels. These bodies are not pathognomonic of lupus erythematosus and may, according to Parsons,[18] be seen as a manifestation of generalized toxemia in leukemia, hypertensive vascular disease, generalized septicemia, optic neuritis, laceration of the retina and increased intracranial pressure with papilledema. Friedenwald stated that they may also occur in severe anemias and terminal carcinomatosis. The nature of these bodies has been disputed. Cone and MacMillan [19] described them as varicose nerve fibers whose cellular detail was lost by subsequent degeneration. Verhoeff [20] described bodies like these in gliomas of the optic nerve and brain and believed that they were swollen neuroglial fibers. Friedenwald [21] studied flat preparations of the human retina stained with periodic acid (Hotchkiss technic) to demonstrate fixed carbohydrate. Although he was unable to find a clue to the origin of cytoid bodies, Friedenwald showed their relationship to the vascular net. His specimens revealed that these lesions in the nerve fiber layer lie at the bifurcation of a terminal arteriole. Their position and configuration mark them as minute ischemic infarcts, and, since no occlusions were found, they are probably secondary to arteriolar spasm.

Maumenee noted that the ophthalmoscopically observed papilledema appeared mild to moderate in microscopic sections. In two cases small hemorrhages were observed in the inner fibers of the nerve fiber layer, and a few red blood corpuscles were seen on the edge of the areas of cytoid bodies. No hemorrhage or exudate was seen in the inner nuclear or the reticular layer. Vascular changes were limited to one case, in which slight hyaline degeneration of the arterial intima, typical of arteriolosclerosis, was present. The ganglion cells were normal, and no subretinal exudation was seen in any of the cases. Mild infiltration of the choroid with round cells was thought to be another manifestation of generalized toxemia, as seen in many types of systemic disease—the septic choroiditis described by von Roth [22] and later by Friedenwald and Rones.[23] In one of this group of four cases serous exudation and hemorrhage into the stroma of the choroid had occurred.

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18. Parsons, J. H., cited by Maumenee.[17]

19. Cone, W., and MacMillan, J. A.: The Optic Nerve and Papilla, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 892.

20. Verhoeff, F. H.: Primary Intraneural Tumors (Gliomas) of the Optic Nerve: A Histologic Study of 11 Cases, Including Case Showing Cystic Involvement of Optic Disc, with Demonstration of Origin of Cytoid Bodies of Retina and Cavernous Atrophy of Optic Nerve, Tr. Sect. Ophth. A. M. A., 1921, p. 146.

21. Friedenwald, J. S.: A New Approach to Some Problems of Retinal Vascular Disease, Am. J. Ophth. **32**:487, 1949.

22. von Roth, M.: Beiträge zur Kenntniss der varicösen Hypertrophie der Nervenfasern, Virchows Arch. f. path. Anat. **55**:197, 1872.

23. Friedenwald, J. S., and Rones, B.: Some Ocular Lesions in Septicemia, Arch. Ophth. **5**:175 (Feb.) 1931.

Koch and McGuire [24] reported a case of acute disseminated lupus erythematosus in a woman aged 22. The clinical diagnosis was not confirmed by necropsy, and hence the ocular findings must be interpreted in the light of this situation. The patient's ocular complaints were blurred vision and decreased visual acuity. Funduscopic examination revealed questionable blurring of the margin of the nerve head and numerous fine to large superficial hemorrhages both in the macula and in the periphery. These were in close proximity to capillaries, swollen arterioles and venules. The vessels showed progressive changes, starting as a periphlebitis, accompanied with deep retinal and choroidal exudates. The perivasculitis became gradually worse and extended to the disk. The hemorrhages and exudates increased, but the older ones tended to be absorbed. The peripheral vessels became fibrous cords with obliterated channels. Primary optic nerve atrophy supervened, and the retina became thin and sprinkled with diffuse granular pigmentation. The patient had no light perception prior to her death.

Cordes and Aiken [25] reported a case with findings similar to those of Koch and McGuire. They concluded that the vascular changes in the retina seen in their patient were probably secondary to superimposed renal changes (not of lupus origin) and hypertension. Koch and McGuire did not record the blood pressure in their case.

*Essential Polyangiitis.*—In only 10 per cent of more than 550 cases of essential polyangiitis in the medical literature was ocular involvement demonstrable. The general pathological picture is one of nonsuppurative inflammation, beginning in the adventitia and media with secondary involvement of the intima. Extensive perivascular infiltration with polymorphonuclear leukocytes, eosinophils and, to a less degree, lymphocytes occurs. If the process extends to the intima of the smaller vessels, they become occluded. Necrosis of the vascular wall may lead to aneurysm of the affected vessels.

Goldsmith [26] reported a case with involvement of the choroidal and retinal arteries. His patient had blurred disk margins, round and linear hemorrhages at the posterior pole, "soft" white exudates, a fusiform aneurysm of the lower temporal retinal artery, irregularities of arterial caliber and congested veins. Microscopically, the hemorrhages and serofibrinous exudates of the retina were seen to lie in the outer plexiform and nuclear layers, especially in the macular region. There was some microcystic degeneration of the retina, and the optic nerve was mildly edematous. The changes in the retinal vessels were minimal.

Focal infiltration with lymphocytes and mononuclear cells was seen around the small arteries of the choroid. The greatly thickened walls revealed fibrinoid degeneration. The endothelial linings were proliferated and the lumens narrowed almost to occlusion. Several of the choroidal vessels showed aneurysmal dilatation. The retina, choroid and ciliary body were partially detached by serous exudate. Goldsmith reviewed the literature and listed the following ocular signs: papilledema with optic nerve atrophy; involvement of the choroidal and retinal vessels with

24. Koch, F. L. P., and McGuire, W. P.: Intra-ocular Manifestations of Acute Disseminated Lupus Erythematosus (Report of Case), Am. J. Ophth. **29**:1243, 1946.

25. Cordes, F. C., and Aiken, S. D.: Ocular Changes in Acute Disseminated Lupus Erythematosus (Report of Case with Microscopic Findings), Tr. Am. Ophth. Soc. **44**:166, 1946.

26. Goldsmith, J.: Periarteritis Nodosa with Involvement of Choroidal and Retinal Arteries, Am. J. Ophth. **29**:435, 1946.

formation of fusiform aneurysms; "retinitis" with retinal detachment, hemorrhages and exudates; recurrent hemorrhages in the vitreous, and involvement of the extraocular muscles. Harbert and McPherson's [27] case of essential polyangiitis is the only one in the literature in which scleral necrosis developed. The diagnosis was confirmed by muscle biopsy. Bock and von Herrenschwand [28] each reported a case in which the central artery was involved.

*Dermatomyositis.*—Another rare disease in this group is dermatomyositis. It it characterized by gradual onset with vague systemic prodromes, followed by scattered areas of edema of the skin and muscular inflammation. Exacerbations and remissions are common, and the course of the disease may run from weeks to several years. Terminal bronchopneumonia is often encountered. Duke-Elder [29] enumerated the ocular signs mentioned in the literature. These include conjunctivitis, iritis, ptosis, paralysis of the extraocular muscles, lateral nystagmus and exophthalmos. Bruce [30] observed three cases with retinitis. Sections were obtained from one of these for histopathological examination. The fundus picture revealed a normal disk and arteries, but the veins were distended. Many superficial exudative deposits were present at the posterior pole and included the macula. The exudates were associated with round and flame-shaped hemorrhages. The lesions tended to become confluent but were resorbed in the cases recovered. Microscopic study revealed marked edema, especially in the inner retinal layers. Varicose nerve fibers were noted. In the outer plexiform layer were albuminous deposits and hemorrhages. The varicose nerve fibers were identical, I assume, with the cytoid bodies described in acute lupus erythematosus by Maumenee and reported in other diseases by various authors.

*Erythema Multiforme.*—Patz [31] reported ocular involvement in 148 of the 162 cases of erythema multiforme in the literature. His analysis revealed that when mucous surfaces are involved, purulent or membranous conjunctivitis is severe. Corneal lesions are frequent, and perforation, with loss of the globe, has been reported. Keratoconjunctivitis sicca and symblepharon are common in this entity.

*Erythema Nodosum.*—Nodules in the conjunctivae bulbi associated with erythema nodosum were recorded in 1939 by Greene and Perry [32] and later by Anthony and Marshall.[33]

The former authors described a white woman aged 54 who had had a tonsillectomy. Her original complaint was "exhaustion." The hypertrophic tonsils had been considered a possible source of infection. Two months after the tonsillectomy a triangular area of hyperemia developed in each eye, with the base abutting on the limbic area and the apex lying over the insertion of the four rectus muscles. In each of these areas two to four nodules developed,

27. Harbert, F., and McPherson, S. D., Jr.: Scleral Necrosis in Periarteritis Nodosa: Case Report, Am. J. Ophth. **30**:727, 1947.

28. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1945, vol. III, pp. 2643-2644.

29. Duke-Elder,[28] p. 2674.

30. Bruce, G. M.: Retinitis in Dermatomyositis, Tr. Am. Ophth. Soc. **36**:282, 1938.

31. Patz, A.: Ocular Involvement in Erythema Multiforme, Arch. Ophth. **43**:244 (Feb.) 1950.

32. Greene, L. S., and Perry, M. W.: Erythema Nodosum with Nodules in the Conjunctivae, Am. J. Ophth. **22**:389, 1939.

33. Anthony, E. W., and Marshall, D.: Erythema Nodosum Episcleritis: Case Report, Am. J. Ophth. **27**:398, 1944.

with a small network of vessels around them. The involved conjunctiva was freely movable over the sclera. Both globes were normal except for the conjunctival lesions. Approximately 12 days after the ocular symptoms appeared there developed painful swelling of the wrist, ankle and knee joints with typical lesions of erythema nodosum on the arms and legs. The Mantoux test gave a negative reaction. The lesions of the extremities and eyes gradually disappeared over a period of four weeks on a regimen of 45 grains (2.9 Gm.) of salicylates daily. Anthony and Marshall's patient, a young man, had conjunctival nodules similar to those of Green and Perry's patient. The ocular lesions were aggravated by withdrawing salicylates, but they were unaffected by changing or discontinuing sulfonamide therapy. This evidence, the authors believed, ruled out drug sensitivity as a basis for the conjunctival lesions. Similar ocular lesions associated with erythema multiforme had been described previously in the literature by Reis, Schieck, Beaudonnett, Weltistscheff, von Rotth, Rameev, Krachmalnikov, Feigenbaum and Carstein.

*Thromboangiitis Obliterans (Buerger's Disease).*—This disease is often included with the collagen diseases. It is a vascular disease of unknown cause in which an acute inflammatory process involves both arteries and veins. Thrombus formation occurs with sequelae secondary to ischemia and anoxemia. The blood vessels of the eyes may be involved, and bleeding into the retina and vitreous may produce changes of such magnitude as to lead to blindness.[34] Birnbaum, Prinzmetal and Connor [35] observed distention and tortuosity of the retinal arteries and veins and compression at the arteriovenous crossings, but no hemorrhages or exudates. Gresser [36] reported bilateral ocular involvement in a man aged 56, who had had a bilateral leg amputation for gangrene. Both optic disks and maculas were edematous, and multiple large, round hemorrhages and areas of degeneration were present in the retinal periphery. The veins and arteries were attenuated, and there was pronounced tortuosity. Segmented columns of blood were seen in the veins, but these gradually disappeared in the left eye. The right eye became glaucomatous. Gresser attributed the occlusion of the arteries and veins to thromboangiitis of the retinal vessels. Marchesani [37] followed the clinical course of three patients with this malady and eventually made microscopic examination of one eye. The primary changes were in the retinal, iris and ciliary vessels. The affected vessels showed swollen tissue in the subendothelial layer and irregular contraction of the lumen. Some of the vessels were filled with granulation tissue. Although Marchesani found that the retinal vascular changes were essentially in the periphery, he noted that the central vessels might become involved to create the picture of thrombosis of the central vein.

*Rheumatoid Arthritis and Allied Conditions.*—Acute attacks of serous, or non-granulomatous, uveitis, episcleritis and scleritis are well known in cases of rheumatoid arthritis. Granulomatous uveitis occurs rarely as a primary phenomenon in this disease but may follow repeated attacks of the serous type. Lesions which retain their serous characteristics are usually resorbed, with few sequelae.

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34. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, pp. 1039-1040.

35. Birnbaum, W.; Prinzmetal, M., and Connor, C. L.: Generalized Thrombo-Angiitis Obliterans: Report of Case with Involvement of Retinal Vessels and Supra-Renal Infarction, Arch. Int. Med. **53**:410 (March) 1934.

36. Gresser, E. B.: Partial Occlusion of the Retinal Vessels in a Case of Thromboangiitis Obliterans, Am. J. Ophth. **15**:235, 1932.

37. Marchesani, O.: Thromboangiitis obliterans am Auge, Arch. f. Augenh. **109**:124, 1935.

Multiple Rheumatoid Arthritis (Still's Disease): In children, a chronic form of polyarthritis of the rheumatoid type occurs and is commonly associated with enlargement of the liver and spleen. In a high percentage of cases there is associated low grade, indolent iridocyclitis with few external inflammatory signs. Characteristically, a band-shaped opacity of the cornea develops.

Chronic Ankylosing Spondylitis (Marie-Strümpell Disease): This condition is thought to differ from rheumatoid arthritis in that it chiefly affects young males and usually starts in the lumbar portion of the spine. The changes in the joints resemble those of rheumatoid arthritis; but, in addition, there is calcification of the longitudinal ligaments of the spinal column. The end result is the classic fused "poker spine." The commonest ocular lesion is serous iritis. The incidence of iritis in Still's and in the Marie-Strümpell disease is higher than that in ordinary rheumatoid arthritis, frequently reaching 50 per cent. It is significant that osteoarthritis is not associated with ocular inflammation.

Grignolo [38] reported a case of a condition which he thought might be intermediate between the group including spondylarthritis and Still's disease and such disorders as Behcet's syndrome and erythema multiforme.

In a man aged 49, who had been afflicted with spondylarthritis for 24 years, acute iritis with hypopyon developed. Puncture of the anterior chamber was performed, but no micro-organisms were found in smear and on culture. Recovery occurred in 10 days after administration of salicylates, sulfonamides and penicillin with protein therapy. Relapse followed in one month, accompanied with erythema multiforme exudativum of the lower limbs, genitals and face.

Scleromalacia Perforans: This condition was designated as a clinical entity by van der Hoeve [39] in a report of four cases in 1934. Verhoeff and King [40] reported one case and summarized the observations in 14 cases, including van der Hoeve's four cases. One case in the series, that of a nonarthritic, 34 year old patient, was "doubtful," the only significant finding being a filtering cicatrix at the corneal limbus. Rheumatoid arthritis was present in 10 cases and absent in four, including the doubtful case. In one case scleroderma and porphyrinuria were present, in addition to rheumatoid arthritis.

The following clinical description of the disease, based on the recorded cases, is taken from Verhoeff and King's excellent paper.

In one or both eyes there developed simultaneously or at intervals slightly elevated nodules involving the sclera and overlying tissue and situated anywhere between the corneal limbus and the equator. Congestion is moderate and is limited to the nodules and their immediate vicinities. After a considerable period, in some cases six months or longer, one or more of the nodules may disappear. At the former site of a nodule there is seen in the sclera a shallow cavity, often of large size. Over a cavity the conjunctiva may be intact or absent. When, as rarely happens, a lesion is situated at the corneal limbus, it may perforate into the anterior chamber and produce a cystoid nodule such as occurs after trephining. Into this nodule the iris may or may not be herniated. When situated elsewhere, the lesions seldom if ever perforate the sclera, and the remaining tissue usually withstands the intraocular pressure, rupturing only in rare instances. . . . Purulent infection [may occur] at the site of a cavity.[40]

38. Grignolo, A.: Über einen bisher noch nicht beschriebenen Symptomenkomplex: Rezidivierende Hypopyoniritis, polymorphes Erythema exsudativum und Spondylarthritis ankylopoietica, Ophthalmologica **118**:989, 1949; abstracted, Excerpta med. XII **4**:446, 1950.

39. van der Hoeve, J.: Scleromalacia Perforans, Arch. Ophth. **11**:111 (Jan.) 1934.

40. Verhoeff, F. H., and King, M. J.: Scleromalacia Perforans: Report of Case in Which Eye was Examined Microscopically, Arch. Ophth. **20**:1013 (Dec.) 1938.

Otherwise, intraocular inflammation is slight or absent. Pain may be absent but is frequently severe. Posterior synechias, atrophy of the iris or cataract may occur as late complications in severe cases. Ocular involvement usually does not start before the patient has reached the age of 50 years. In the great majority of cases definite evidences of rheumatoid arthritis exist at the outset of the scleritis.

The histological changes in their case pointed to primary necrosis of scleral tissue in a sharply defined area. This area becomes surrounded by a wall of epithelioid cells and is slowly infiltrated with pus cells. This process results in formation of a sequestrum, which becomes completely disintegrated and densely infiltrated with pus cells. Thus an abscess is formed in the sclera, which corresponds in position to the nodules observed clinically. The characteristic cavities in the sclera are due to perforation of these abscesses and extrusion of their contents. At the site of an abscess there remains a thin layer of newly formed fibrous tissue with pigment cells in the deeper layers. Verhoeff and King believed it is possible that fibrous tissue replacement of necrotic tissue may occur without the formation of cavities. Histologically, in the initial stages the scleral nodules are similar to the subcutaneous nodules of rheumatoid arthritis. Obliterative endarteritis in the vicinity of the abscesses suggested that anemic necrosis was the cause of abscess formation. However, Verhoeff and King concluded that the vascular changes may have resulted from, rather than caused, the inflammatory changes.

Smoleroff [41] reported three cases of rheumatoid arthritis complicated by scleral lesions. Histologic study of both eyes in one of his cases showed large abscesses deep in the substance of the sclera and multiple minute areas of necrosis and cellular reaction. These findings were comparable to those described by Verhoeff and King. No micro-organisms were demonstrated in either case.

Nodular Episcleritis: This condition associated with chronic rheumatic polyarthritis in a white man aged 56 was described by Edström and Österlind.[42] Histological examination of a nodule excised from the left eye revealed normal conjunctival epithelium overlying the granulomatous mass. Collagenous fibrils became more swollen and disintegrated as they approached the center of the mass. Actual connective tissue necrosis was noted centrally. At the periphery were collections of large "fibroblastoid" cells, often in radiate formation. Plasma cell infiltrates were present in adjacent connective tissue. At autopsy similar changes were seen around myocardial blood vessels, heart valves and in the periarticular tissues.

The association of intraocular inflammation with acute inflammatory changes in the joints produced many etiological theories, one of the most popular being that of the "focus of infection." Woods [43] reviewed the evidence for and against the theory of focal infection and the relation of secondary ocular infection to a remote primary focus of infection. He concluded that in the present state of knowledge all that can be said is that experimental studies indicate that the eye may become sensitized by bacterial seeding from the blood stream. These organisms need not

41. Smoleroff, J. W.: Scleral Disease in Rheumatoid Arthritis: Report of Three Cases, in One of Which Both Eyes Were Studied Post Mortem, Arch. Ophth. **29**:98 (Jan.) 1943.

42. Edström, G., and Österlind, G.: A Case of Nodular Rheumatic Episcleritis, Acta. ophth. **26**:1, 1948.

43. Woods, A. C.: Focal Infection, in Sorsby, A.: Modern Trends in Ophthalmology, London, Paul B. Hoeber, Inc., 1947, vol. 2, p. 209.

originate in a clinically infected focus but may gain entry via any mucous membrane. Subsequently, repeated exposure of the sensitized tissue to these bacteria or their products from a remote focus may produce ocular inflammation. It is possible that the eye and the joints may be involved simultaneously in this type of hypersensitivity response to a focus of infection.

## COMMENT

The ocular findings in the group of diseases described in this paper are not diagnostic. The common factors of involvement of blood vessels and collagen degeneration may account for the ocular signs in both the systemic diseases with associated ocular manifestations and in a disease like scleromalacia perforans, in which the findings are predominantly in the eyes. The pathogenesis is clearer in entities with demonstrable vascular change than in those with minimal pathologic change in the blood vessels. In the latter, connective tissue injury is probably secondary to other factors. The precise nature of the pathological physiology is unknown. In order to comprehend the dynamics of this problem, it will be necessary, perhaps, to know the chemical constitution of the ground substance and the influence of blood supply, enzymes and hormones, such as ACTH and cortisone, on its reactivity.

The fact that degeneration of scleral fibers, rather than vascular change, is the striking feature in scleromalacia perforans suggests that there may be other ocular conditions unassociated with systemic disease which show primary connective tissue alterations in extravascular tissues. The subepithelial tissue of the conjunctiva, sclera, episcleral tissue, extraocular muscle sheaths and tendons, corneal stroma, anterior chamber filtration angle meshwork, and the stroma of the iris, ciliary body and choroid have varying amounts of connective tissue elements. The septal system of the optic nerve and the dural, arachnoidal and pial sheaths have collagenous components. The retinal vessels are enveloped by connective and neuroglial tissue continuous with that of the optic disk. It is interesting to speculate that alterations of connective tissues may be responsible wholly or in part for such conjunctival diseases as pemphigus, amyloid degeneration and rosacea keratoconjunctivitis. Corneal involvement in Fuchs's marginal dystrophy, Mooren's ulcer, pterygium and keratoconus may represent a degeneration of fibrillar, cellular or interfibrillary elements. Other ocular disease entities that might be considered in these terms are wide angle glaucoma, essential atrophy of the iris and choroid, angioid streaks, Eales's disease and malignant myopia.

## SUMMARY

The development of the concept of diffuse collagen disease is presented, with a review of the morphology, physiology and chemistry of connective tissue. The nature of the response of these tissues to injury and the characteristics of fibrinoid degeneration are described.

The general pathological characteristics and the ocular manifestations of these diseases are presented. It is submitted for consideration that, just as there is ocular involvement in these diseases with generalized connective tissue alterations, so may there be purely ocular diseases due to alterations of the local mesenchymal derivatives.

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# PHYSIOLOGICAL CONSIDERATIONS OF ACTH AND CORTISONE THERAPY WITH REFERENCE TO OPHTHALMOLOGY

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IN PRESENTING this study on ACTH and cortisone, we thought it wise, in accordance with the advice of Dr. Justin Donegan, to describe briefly these products from a chemical and biologic viewpoint and then to turn to their physiological properties relevant to their use in ophthalmologic problems. Certain of these properties work for healing; others, unless proper safeguards are taken, give rise to complications.

## CHEMICAL AND BIOLOGIC ASPECTS

ACTH, as the initials imply, is an adrenocorticotropic hormone. Formed in the pituitary, the currently available products are extracted from hog and beef glands, separated from other hormones and concentrated by the comparatively tedious methods of the protein chemist. ACTH, like other pituitary "-tropic" hormones (e. g., thyrotropic and gonadotropic), is a protein.[1]

Synthetic production of ACTH has not been achieved, although activity has been demonstrated in some peptide fractions of low molecular weight containing only about eight amino acid residues. Such a typical protein hormone molecule as insulin is about 30 times the size of this type of peptide. Although presumably not antigenic, these peptide products are not available for clinical use.

In contrast to hormones of pituitary origin, and like other hormones extracted from the adrenal gland and the gonads, cortisone is a steroid. Considering that there exist steroid hormones of precisely opposite biologic effects, e. g., estrogens and androgens, and that certain steroids have no direct hormonal effect, e. g., cholesterol, it is a matter of continued wonder that all these compounds have a

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Presented at a meeting of the Chicago Ophthalmological Society, Oct. 2, 1950 as part of a symposium on ACTH and cortisone.

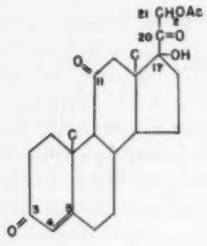
From the Rush Department of Medicine of the Presbyterian Hospital of the City of Chicago and the University of Illinois College of Medicine.

We wish to acknowledge support from the Otho S. A. Sprague Memorial Institute of Chicago in our work in the investigation of the mechanism of these drugs.

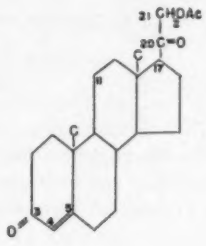
1. The product presently available has exhibited in rare instances the most troublesome effects of a protein from an animal species when given to man, namely, the setting up of an allergic reaction. Since here the protein nature of the ACTH, in producing allergy, acts in a direction opposite to that of one of its adrenal-mediated hormonal effects, namely the blocking of certain allergic manifestations, a curious seesaw of clinical phenomena may be encountered. A description of allergic reactions to ACTH will be found in the *Proceedings of the Second Clinical ACTH Conference,* 1950, edited by John R. Mote, Philadelphia, The Blakiston Company, to be published.

common structure, a four ring arrangement of some 18 carbon atoms. The varied biologic effects are correlated with various chemical groups attached to certain of these atoms.

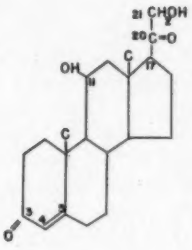
This may be simply illustrated by three adrenal hormones, whose structural formulas are given in the accompanying chart. At the upper left is cortisone, whose healing effects in certain ocular diseases will be discussed in this symposium. At the upper right is desoxycorticosterone, which has no healing effects whatever on




CORTISONE ACETATE
(11-DEHYDRO-17-HYDROXY CORTICOSTERONE)




DESOXYCORTICOSTERONE ACETATE




CORTICOSTERONE
(COMPOUND B)

Three hormones of the adrenal gland.

inflammation, but which has been of great clinical use in treating metabolic disturbances of Addison's disease (in which the adrenal gland is either destroyed or otherwise incapable of function). The chemical differences are at the carbon atoms carrying the numbers 11 and 17. Desoxycorticosterone has no oxygenated groups at 11 and 17; cortisone has a double-bonded oxygen (ketone) at 11 and a hydroxyl group at 17. Corticosterone, one of the first adrenal hormones worked out by Kendall, is illustrated at the bottom of the figure. This differs from cortisone in having a hydroxyl group at 11 and no oxygen at all at 17.

The great biologic differences consequent on these seemingly small chemical ones can be further illustrated by contrasting the effects of cortisone and desoxycorticosterone in the patient with Addison's disease.

Desoxycorticosterone causes the kidney to retain sodium and lose potassium. Cortisone has the same effect but to a far less degree, milligram for milligram of hormone. Desoxycorticosterone has no effect whatever on carbohydrate metabolism; it does not restore the flat glucose tolerance curve often seen in Addison's disease, nor does it prevent hypoglycemic attacks. Cortisone, *per contra,* restores normal glucose tolerance in Addison's disease and can prevent hypoglycemia. In normal subjects prolonged administration of large doses leads to a diabetic state, which usually disappears when therapy is stopped. If this diabetes is uncontrolled, it serves as a second mechanism of excessive urinary loss of potassium.

Again in Addison's disease there are definite cerebral changes, which can be shown by the behavior of the patient and by electroencephalograms. These are not reversed by desoxycorticosterone; they are reversed by cortisone.

When ACTH is given to a patient, the adrenal gland secretes a whole series of hormones, of which those illustrated in the figure are merely the best known. Thus, there is a salt-retaining effect, a potassium loss effect, a cerebral effect, and an effect on glucose tolerance, all of which become important in long term therapy. Dr. Donegan, who has had wide experience with these materials in therapy of ocular disease by systemic administration, will tell you that long term therapy may cause trouble. We can tell you, from our own experience in long term therapy, that ACTH when used for five or six months without proper precautions can produce dangerous illness, and in some instances death. We shall mention later some of the precautions we have to take in systemic ACTH-cortisone therapy to prevent these complications.

The effects we have thus far discussed are in the main metabolic, and it was in metabolic terms that the potential uses of ACTH were first considered when the first large scale preparations of Armour Laboratories were put in the hands of clinical investigators by Dr. John R. Mote, about three years ago.

It is true that Selye's concept of the adrenal cortex as related to the adaptation of the body to stressful situations took cognizance of inflammatory phenomena, but facts initially were few. Ten years ago, a group of workers on the dermatological and medical services of the Massachusetts General Hospital, in studying disturbances of electrolyte metabolism reminiscent of Addison's disease in pemphigus, had made the remarkably prophetic observation that the bullous, serum-filled cutaneous lesions in this often fatal disease improved on appropriate electrolyte administration plus use of whole adrenal extract; on electrolyte therapy alone, "continued clinical improvement invariably ceased following withdrawal of the extract."[2] For most workers, these findings remained buried in the dermatological literature until recently exhumed by hindsight. There were few grounds for the prediction of a favorable effect of adrenal hormones on inflammation, such as the rapid resolution of acute iridocyclitis of unknown etiology, until the publication by Hench and his co-workers about two years ago of their epoch-making observations on the effect of ACTH and cortisone in inflammatory joint diseases. Since then,

2. Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies on Patients with Pemphigus, J. Invest. Dermat. **3**:31-68, 1940.

these drugs have been applied in almost every type of inflammatory state, with extraordinarily variable, and sometimes extremely valuable, results.

Here an interesting therapeutic paradox has emerged. The very properties of adrenal steroids which work for the patient with Addison's disease work against the patient under long term therapy for healing of inflammatory lesions. Despite metabolic precautions, such a patient will sometimes show a gain of too much salt and water, yielding edema, or loss of too much potassium, yielding muscular weakness, abdominal cramps and a deranged electrocardiogram, or will at length take on the full blown Cushing syndrome (obesity with characteristic purple striae, hirsutism and diabetes with excessive nitrogen loss), which is encountered clinically in some instances of tumor or hyperplasia of the adrenal gland with excessive spontaneous adrenal steroid secretion. Long term systemic therapy with ACTH or cortisone can lead to a precarious clinical balance—between metabolic effects approaching toxicity, on the one hand, and a dose inadequate to control inflammatory phenomena, on the other.

Fortunately, the problems of this balance are not as important in ophthalmology as in clinical medicine, for two reasons:

1. The eye is readily available for local therapy, and effective high local concentrations of cortisone have been achieved to give remarkable therapeutic results without sufficient general absorption to produce untoward metabolic effects. (ACTH, of course, is not effective locally, since its action demands that it reach a functioning adrenal gland.)

2. The diseases in which therapy has been most effective have, in their natural courses, been sufficiently cyclical and/or self limited that the prolonged courses of medication often needed in internal medicine can be avoided.

## THERAPEUTIC CONSIDERATIONS

The effects of cortisone, whether of exogenous or of endogenous (ACTH-stimulated) origin, on inflammatory phenomena may now be briefly reviewed.

1. Cellular exudation is reduced, with respect to neutrophilic polymorphonuclear leukocytes, round cells and eosinophils. This has been illustrated by serial biopsies in a wide variety of types of inflammation.

2. The permeability of capillaries to proteins in regions of inflammation is reduced. This may be illustrated quantitatively in a patient with scleredema. This rare disease of the skin (not to be confused with scleroderma) presents a generalized, brawny edema of the skin. Vesicles on the lower extremities provide a source of small quantities of the edema fluid for protein determinations by micromethods. Before treatment, the protein content of the fluid in these vesicles was about 2.5 Gm. per 100 cc. After administration of ACTH, the protein content fell to under 0.5 Gm. per 100 cc; the latter values approach those found for transudates, e. g., the edema fluid of a patient with cardiac disease rather than for exudates.

3. The development of an intense fibrotic reaction in the course of healing is lessened. This can be illustrated in the field of internal medicine by scleroderma, which, as its name implies, is a stiffening of the skin due to the laying down of a great deal of collagen without much edema. A clinical softening is associated with breaking up of these collagen bundles, as seen microscopically.

Again, in the field of surgery, profuse proliferation of granulation tissue, which in many third degree burns ultimately leads to contractures, appears to be strikingly decreased under ACTH therapy.

Although these results are beneficial, the same effect on weakening of fibrous repair can be deleterious to the healing of surgical wounds in patients under intensive ACTH and/or cortisone therapy. This is seen notably in wounds at the site of removal of biopsy specimens of skin from areas subject to stretch and in abdominal wounds subject to the stress of coughing and straining.

All organs are not identical in terms of the response of inflammatory phenomena. Thus, in internal medicine, at one extreme, remarkable effects of ACTH therapy have been achieved in treatment of the myocarditis of acute rheumatic fever, a disease whose mechanism is believed to be related to hypersensitivity. At the other extreme, almost no clinical effects have been observed on the course of acute clinical glomerulonephritis, whose mechanism is also believed to be hypersensitivity.[3]

Inflammations of the eye, whether due to direct bacterial invasion, to hypersensitivity to foreign proteins or even to certain chemical irritants, have proved unusually sensitive to blocking by cortisone. If, however, the animal is hypersensitive to a foreign protein, when the effect of cortisone has worn off, inflammation can be produced to an extent equal to that possible before use of cortisone.

Such results are quite consistent with studies on the inflammatory reaction in otner situations, in that inflammation will recur if during the time of suppression of inflammatory phenomena the cause if known is not removed, or if unknown does not subside spontaneously.

In direct bacterial infection, the last fact is of paramount importance in illustrating further the double-edged nature of ACTH and cortisone therapy. In inflammatory disease of hypersensitive mechanism, that is, when there is no direct infection at the site of the inflammation, and therefore the inflammatory reaction has no obvious function as a body defense, the results of therapy are strikingly beneficial, even though the benefit may be short lived. The duration of benefit depends on whether it is possible during therapy to eradicate the source of the offending material setting up the reaction.

Thus, administration of ACTH to a patient in status asthmaticus has proved a valuable tool in permitting the clinician to study the bacterial flora of the respiratory tract after relief from chronic suffocation. If, however, no related infection is found and eliminated, and there is no clue to the role of inhaled allergens, the asthma is quite likely to recur on cessation of ACTH treatment. The same consideration may be presumed to apply to pathological processes in the eye.

When the inflammatory reaction has a defensive function, that is, when infection exists in the inflamed tissue, the action of ACTH and/or cortisone can be clearly deleterious. ACTH and cortisone are not antibiotics, nor does their use supplant proper chemotherapeutic or surgical treatment of infection. During the last year at the Presbyterian Hospital we have seen several instances, often at the autopsy table, of serious bacterial infections (suppurative pericarditis, sinusitis, cortical renal abscesses) which were clinically unsuspected in patients under treatment for the suppression of inflammatory phenomena in organs other than those in

3. It has proved possible to block the development of certain types of experimental glomerulonephritis by pretreatment.

which the infection was found. This masking of the usual clinical signs of acute inflammation, e. g., fever, redness, tenderness and pain, thus provides a serious problem in the diagnosis of abdominal pain in patients under systemic therapy with ACTH and cortisone.

Suppression of fibrosis following inflammation can also be deleterious. In pulmonary tuberculosis such suppression may well have contributed to miliary spread in a few patients under therapy for various reasons. Such an effect demands serious consideration in appraising the wisdom of the use of these drugs on the exudative phenomena of sites directly infected with the tubercle bacillus, e. g., tuberculous laryngitis, where rapid regression can be obtained. A thorough survey must be made in each case to ascertain the absence of lesions in other places from which miliary spread might be anticipated on clinical grounds.

The mechanisms of these effects on inflammatory phenomena are by no means well understood. In the instance of inflammation associated with allergy, there has been no evidence, on the one hand, of a histamine-blocking effect; on the other hand, although some workers have shown experimentally a decrease in antibody production under ACTH or cortisone therapy, others have demonstrated the blocking of the development of lesions in the presence of specific antibodies against the involved foreign protein and of adequate complement. No defect of antibody-antigen union in vitro has yet been demonstrated.

An observation which may be of import in terms of mechanism with respect to the eye is the inhibition of the enzyme hyaluronidase. This enzyme can break down a polysaccharide of large molecular weight, hyaluronic acid, which is present in some tissues of the eye in high concentration. This effect has been demonstrated experimentally. If a rabbit is given an intravenous injection of trypan blue, the foot pads will not turn blue; if given an injection of trypan blue and hyaluronidase, the foot pads will turn blue, and if given enough of the dye, all the skin will turn blue. On the other hand, if cortisone is injected prior to hyaluronidase and trypan blue, nothing of the kind occurs.

The ophthalmologist is in a particularly fortunate position with reference to many of the deleterious effects noted above. First, as we pointed out before, the organ on which he wishes to work is readily available for local cortisone therapy, and, in general, he will be able to avoid the systemic therapy which has given rise to most of the metabolic and other complications. If, in point of fact, systemic therapy is necessary, few complications are encountered if therapy is limited to 10 days. If therapy beyond this period is indicated by the nature of the disease process in the eye, the simple precaution of a diet low in sodium (with no salt used in cooking and no shaker at the table) and the addition of 3 Gm. of potassium chloride or potassium bicarbonate by mouth has been found by many clinics to be satisfactory for the prevention of hypopotassemia or excessive retention of sodium chloride and water. The simplest means by which the practicing ophthalmologist may keep track of the latter phenomenon is a scale at the patient's home. A gain of weight of 3 pounds (1.3 Kg.) or more in the first week demands investigation and usually means that the dietary regimen has not been followed. These dietary precautions, together with a constant awareness of the masking of infection by systemic therapy and the use of a good bacteriologic laboratory, will, in general, keep the patient out of trouble.

The advantages to be gained in various clinical situations encountered in ophthalmology will be discussed in the ensuing papers, and they are indeed striking. One point is worth emphasis from the standpoint of ophthalmic surgery. A great many inflammatory phenomena consequent on surgical procedures are strikingly decreased if the operation is carried out under ACTH therapy. On the other hand, in procedures in which strength of adhesion is desired, e. g., in the operative treatment of detached retina, it may well prove that the administration of ACTH and/or cortisone is contraindicated. In our clinic, in collaboration with the ophthalmologic service, we have seen a detached retina regain apparently satisfactory position with ACTH therapy, only to have another detachment occur at another site after cessation of therapy.

This, in general, is a brief picture of what ACTH and cortisone do. There are other effects of ACTH not manifested by cortisone. ACTH stimulates the adrenal to produce whole sections of hormones—how many is not yet known. Experience in systemic therapy has shown that there are certain types of dermatological disease which cannot be altered with cortisone, but which are favorably influenced with ACTH. On the other hand, ACTH gives serious, and sometimes dangerous, effects (e. g., psychoses) not seen to such a degree with cortisone therapy.

With reference to the forms of the drugs available for systemic therapy, ACTH, as now available, must be given four or five times a day, owing to its rapid destruction in the body. Preparations are currently under investigation aimed at making possible the continued release of ACTH from the injection mass. The early results of their use have been varied. More recently, preparations permitting one injection every 12 hours have been released on an experimental basis. It is possible that these may soon become generally obtainable.

When cortisone is given systemically, one injection a day, or in prolonged therapy occasionally one injection every two days, is now sufficient. There is coming into use a preparation for oral use which in its early trials is approximately as effective, milligram for milligram, as is the preparation for parenteral use. The preparations for local ophthalmic use will be described in detail in papers which follow.

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Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, to be published.

Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R., Jr.; Roche, M.; Staehelin, D., and Wilson, D. L.: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783-793, 824-834, and 865-872, 1950.

Excellent descriptive material has become available from Armour and Company, of Chicago, on ACTH and from Merck & Company, Inc., Rahway, N. J., on cortisone. This may be obtained by writing to the medical directors of these corporations.

# EFFECT OF CORTISONE ON HORSE SERUM UVEITIS IN RABBITS

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THERE have been numerous clinical reports of the beneficial effect of pituitary adrenocorticotropic hormone (ACTH) and cortisone on inflammatory ocular disease in humans. However, when the present study was begun, relatively little work had been reported on the results of cortisone or ACTH treatment of experimental uveitis. The intraocular injection of horse serum has been found to be a satisfactory method of producing a granulomatous type of uveitis in rabbits,[1] probably on the basis of an anaphylactic type of hypersensitivity. In view of the fact that ACTH and cortisone suppress many forms of systemic hypersensitivity, including cardiovascular lesions in rabbits induced with horse serum,[2] it might well be expected that these substances would be effective in horse serum uveitis. Since the present work was begun, Woods [3] has reported the dramatic effects of ACTH and cortisone on experimentally produced ocular inflammation in rabbits, including the injection of horse serum into the anterior chamber. Histopathological studies were not reported.

In the present study, the uveitis produced by the intravitreal injection of horse serum in previously sensitized rabbits was treated by the systemic administration of cortisone. Both clinical and histological effects are evaluated.

## MATERIALS AND METHODS

A total of 13 mongrel rabbits approximately 15 weeks old were selected in which there was no evidence of preexisting spontaneous uveitis. In previous investigations both active and inactive uveitis have been detected in presumably normal rabbits by examination with the slit lamp and ophthalmoscope. These 13 selected rabbits were then sensitized systemically by the intravenous injection of 10 cc. of normal horse serum.[4] Eight days later, on the ninth day of the

From the Department of Ophthalmology of the University of Illinois College of Medicine.

1. (*a*) Filatov, W.: Über den Einfluss des normalen und immunolytischen Serums auf Auge, Klin. Monatsbl. f. Augenh. **46**:98, 1908. (*b*) Schlaegel, T. F., Jr., and Davis, J. B.: The Reaction of the Rabbit Eye to Normal Horse Serum: Sensitization by Intradermal Injection, Am. J. Ophth. **26**:785-798, 1943. (*c*) Foss, B.: Experimental Anaphylactic Iridocyclitis, Acta path. et microbiol. Scandinav., 1949, supp. 81.

2. Berthrong, M.; Rich, A. R., and Griffith, M. P. C.: Study of the Effect of Adrenocorticotropic Hormone (ACTH) upon the Experimental Cardiovascular Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **86**:131-140, 1950.

3. Woods, A. C.: Clinical and Experimental Observations on the Use of ACTH and Cortisone in Ocular Inflammatory Disease, Am. J. Ophth. **33**:1325-1348, 1950.

4. The horse serum used in this experiment was furnished by Eli Lilly & Company, Indianapolis. It was filtered but contained no preservatives or other added materials.

experiment, the precipitin titer to horse serum was determined on the heart blood by means of the serum dilution ring method. The titers are recorded in the accompanying table. The rabbits to be treated with cortisone and those to serve as controls were selected in such a way that the average titer (calculated logarithmically) would be approximately the same in the two groups.

*Precipitin Titers in Cortisone-Treated and in Untreated Rabbits with Horse Serum Uveitis*

| Rabbit No. | Ninth Day | | Twenty-Third Day | |
|---|---|---|---|---|
| | Titer | Log 1/Titer | Titer | Log 1/Titer |
| **Cortisone-Treated Rabbits** | | | | |
| 5c | 1:100 | 2 | 1:10,000 | 4 |
| 2c | 1:10,000 | 4 | 1:1,000 | 3 |
| 7c | 1:100 | 2 | 1:10,000 | 4 |
| 12c | 1:100 | 2 | 1:10,000 | 4 |
| 4c | 1:1,000 | 3 | 1:100,000 | 5 |
| 9c | 1:1,000 | 3 | | |
| 1c | 1:1,000 | 3 | Average | 4 |
| | Average | 2.71 | Antilog | 10,000 |
| | Antilog | 513 | Average titer | 1:10,000 |
| | Average titer | 1:513 | | |
| **Controls** | | | | |
| 10c | 1:1,000 | 3 | 1:100,000 | 5 |
| 11c | 1:10,000 | 4 | 1:10,000 | 4 |
| 8c | 1:10 | 1 | 1:100,000 | 5 |
| 10c | 1:1,000 | 3 | 1:100,000 | 5 |
| 6c | 1:100 | 2 | | |
| 19c | 1:1,000 | 3 | Average | 4.75 |
| | Average | 2.67 | Antilog | 56,230 |
| | Antilog | 468 | Average titer | 1:56,230 |
| | Average titer | 1:468 | | |

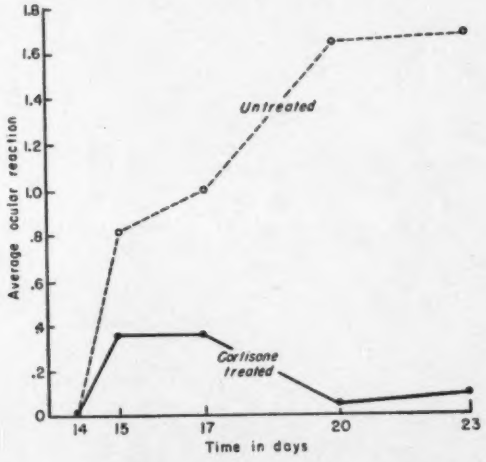


Fig. 1.—Effect of treatment with cortisone on clinical ocular reaction in horse serum uveitis of rabbits.

On the thirteenth day of the experiment the following daily injections were begun: cortisone acetate, 25 mg. per kilogram of body weight, intramuscularly to seven experimental rabbits, and isotonic sodium chloride solution, 1 cc. per kilogram intramuscularly to the six control rabbits. These injections were continued until the animals were killed. Each rabbit was weighed on the

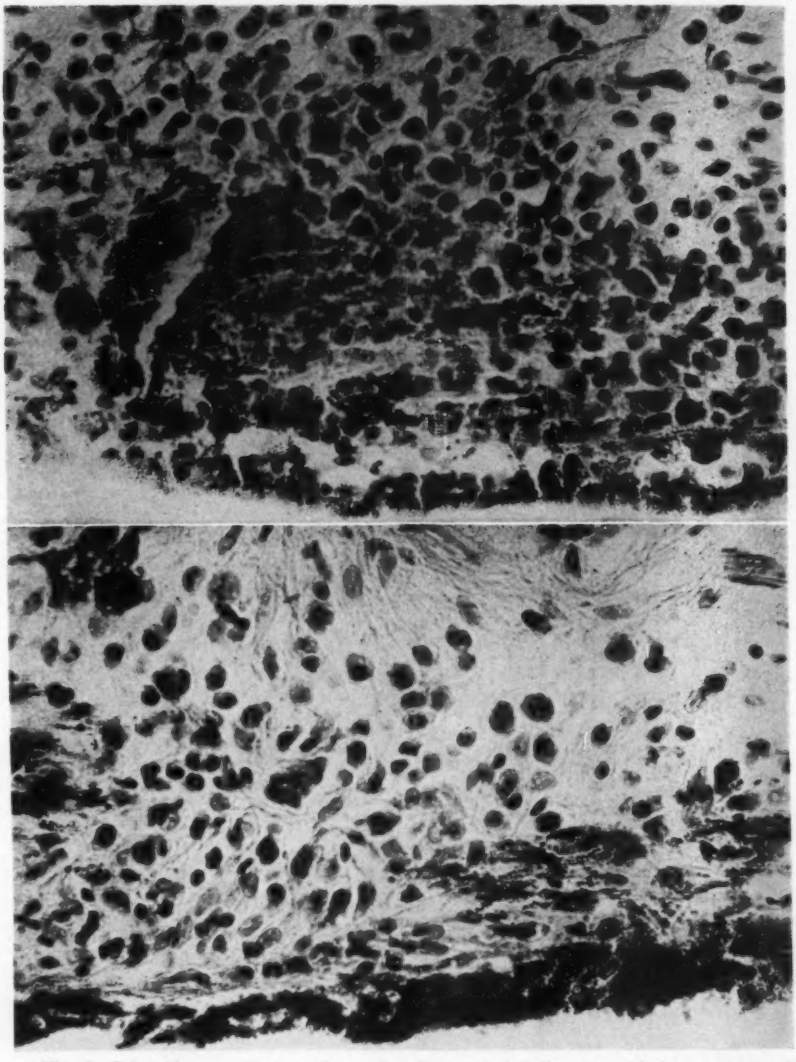

Fig. 2.—Iris. Above, early control eye, showing marked infiltration with immature round cells. Below, early treated eye, demonstrating striking immaturity of inflammatory cells.

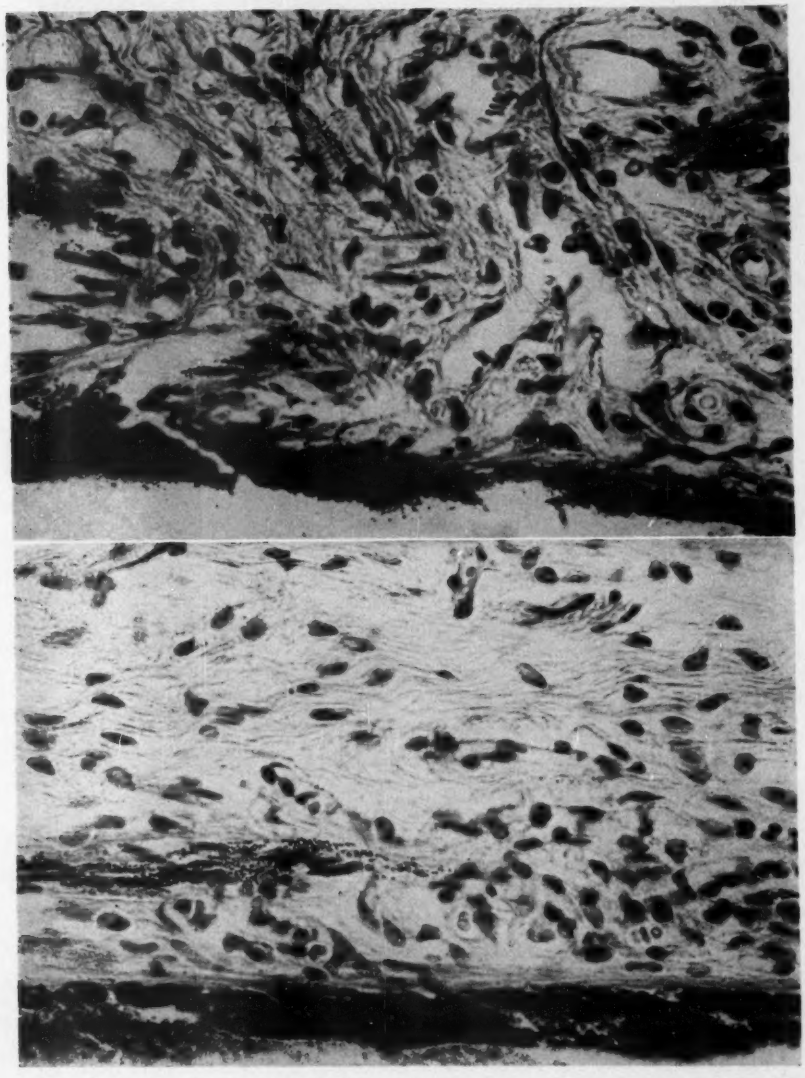

Fig. 2 (cont.).—Above, late control eye, showing hyperemia and/or neovascularization. There is moderate infiltration with mature round cells. Below, late treated eye, showing normal iris stroma with a few round cells near the pigment epithelium.

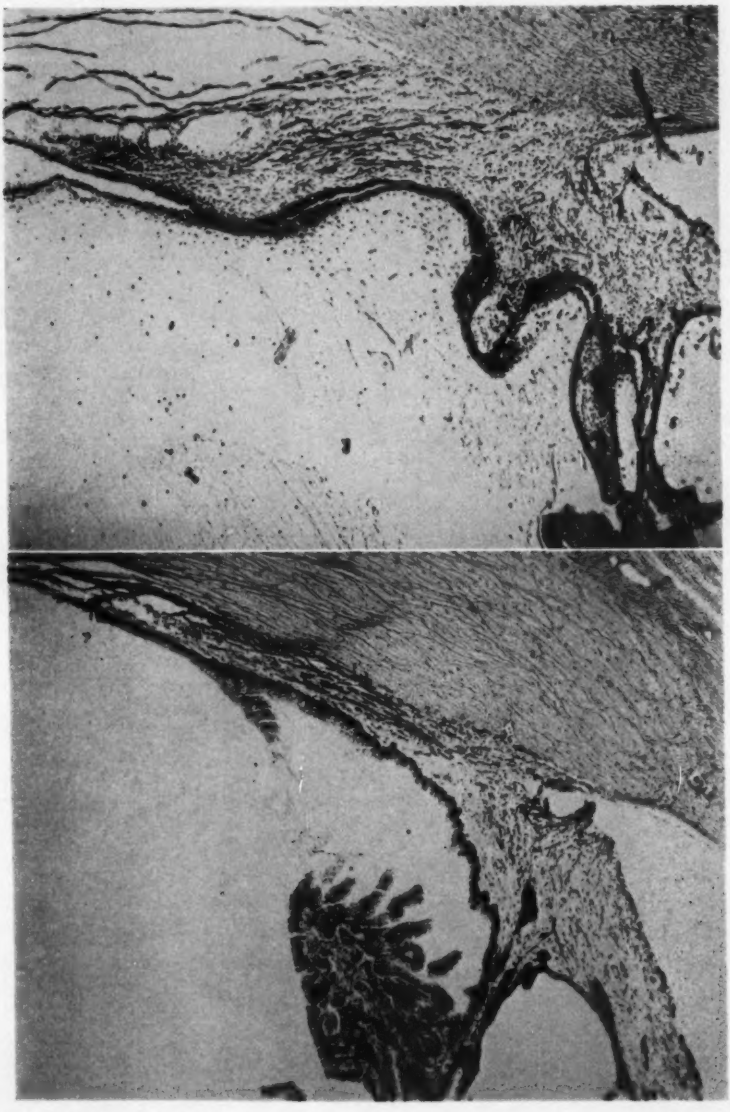

Fig. 3.—Ciliary body and adnexa. Above, late control, least severe reaction. There are a few inflammatory cells at the chamber angle (upper right) and in the posterior chamber (upper right), consisting chiefly of large mononuclear cells and polymorphonuclear leukocytes. The ciliary body is hyperemic and infiltrated with round cells. There are moderate proliferation of ciliary epithelium and cyclitic membrane formation. Below, late treated, least severe reaction, showing normal appearance.

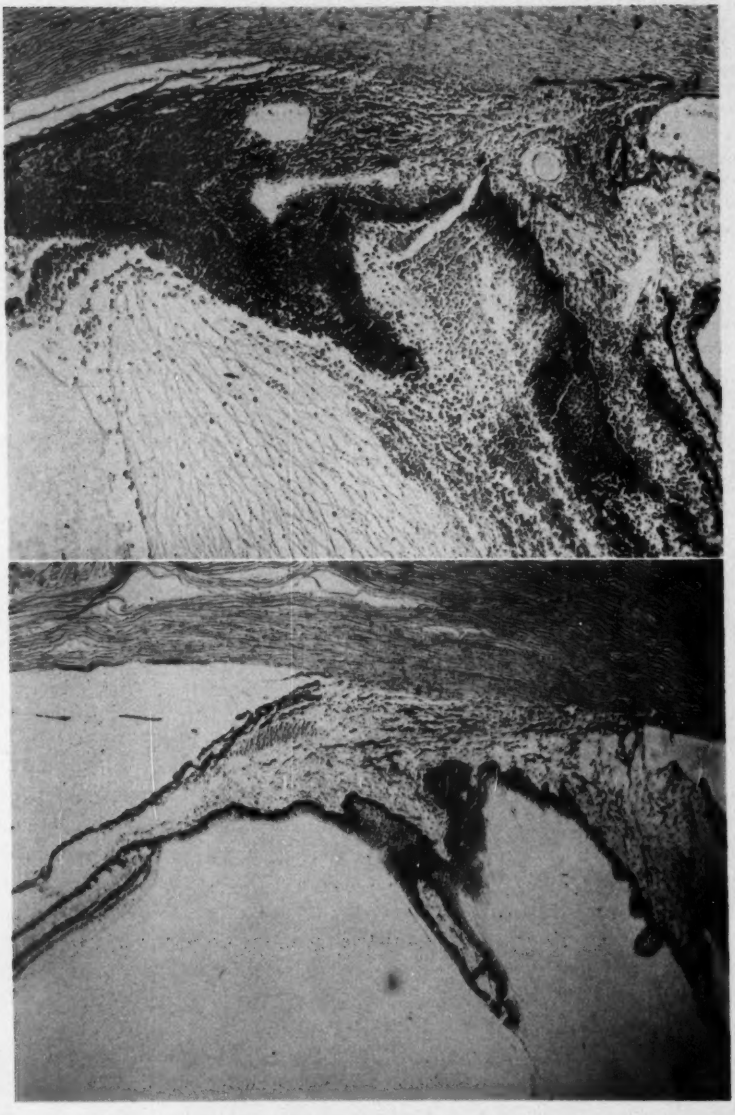

Fig. 3 (cont.).—Above, late control, most severe reaction. There are marked hyperemia, round cell infiltration, proliferation of epithelium and derangement of pigmented border. A pronounced cyclitic membrane, containing round cells, polymorphonuclear leukocytes, fibroblasts and fibrinous material, is present. Below, late treated, most severe reaction, with only mild round cell infiltration.

first, fourteenth and twenty-second days. On the fourteenth day, horse serum was injected intravitreally in each eye of each rabbit by the following technic: After two instillations of 2 per cent tetracaine hydrochloride in benzalkonium chloride solution (1:10,000), the episclera was grasped with forceps about 4 mm. back of the upper limbus, and a 22 gage needle on a tuberculin syringe was inserted into the globe 2 to 3 mm. behind the equator, with special care to avoid hitting the lens. About 0.1 cc. of horse serum was introduced, and the needle was then withdrawn abruptly. Owing to the intraocular pressure, an appreciable amount of the horse serum was extruded into the conjunctival sac and Tenon's space. The eye was immediately examined with the ophthalmoscope to determine whether horse serum had actually entered the vitreous, as evidenced by a small streak of faint, dustlike vitreal opacities, representing the location of the horse serum, and a white spot, of about ½ disk diameter, corresponding to the hole in the choroid and retina produced by the needle. The lens was examined to assure that it had not been struck with the needle.

On the sixteenth day two rabbits from the treated group and two rabbits from the control group were killed by intravenous injection of pentobarbital sodium U. S. P. and their eyes enucleated for histological study. These rabbits were selected on the basis of their possessing the severest uveitis in their group, in order that definite cellular changes in the microscopic sections might be assured. These rabbits are hereinafter designated as early treated and early control groups. On the twenty-third day (the last day of the experiment) the remaining animals (late treated and late controls) were killed by intravenous injection of pentobarbital. The eyes were enucleated and samples of heart blood were obtained for precipitin titer determinations.

The course of the uveitis was observed with the slit lamp and ophthalmoscope on the fifteenth, seventeenth, twentieth and twenty-third days. The reactions were graded + to ++++ for the following signs: aqueous ray, deposits on the anterior capsule of the lens and vitreous haze. The streak of fine, dustlike haze resulting from the injection of horse serum was not included in the grading.

## RESULTS

*Ocular Examinations.*—The course of the uveitis for the late treated and the late control group is plotted in figure 1 for the composite of the gradings for aqueous ray, deposits on the anterior capsule and vitreous haze. This graph reveals that the rabbits treated with cortisone exhibited a milder uveitis than did the controls. The effect was considerably more striking toward the end of the experiment. On the fifteenth and seventeenth days the difference between the treated and the control eyes was not quite statistically significant ($P = >0.1$ by means of the $t$ test), whereas on the twentieth and twenty-third days the difference was significant ($P = <0.01$). The analysis of vitreous haze alone showed a striking inhibition by the cortisone, since none of the treated eyes exhibited vitreous haze of any degree while the vitreous of all the untreated eyes eventually became cloudy. Deposits of cells and fibrin on the anterior capsule were suppressed significantly by cortisone from the beginning, whereas the aqueous ray was not significantly reduced until the last few days of the experiment.

*Histological Effects.*—The histopathological changes in horse serum uveitis in rabbits have been described by Schlaegel.[1b] Some of the more important effects of cortisone on this inflammatory reaction will be described. Eyes of cortisone-treated rabbits showed in general considerably less cellular inflammatory reaction than did the controls. Most of the accompanying photomicrographs are taken from the late groups, since the early groups showed a less striking difference

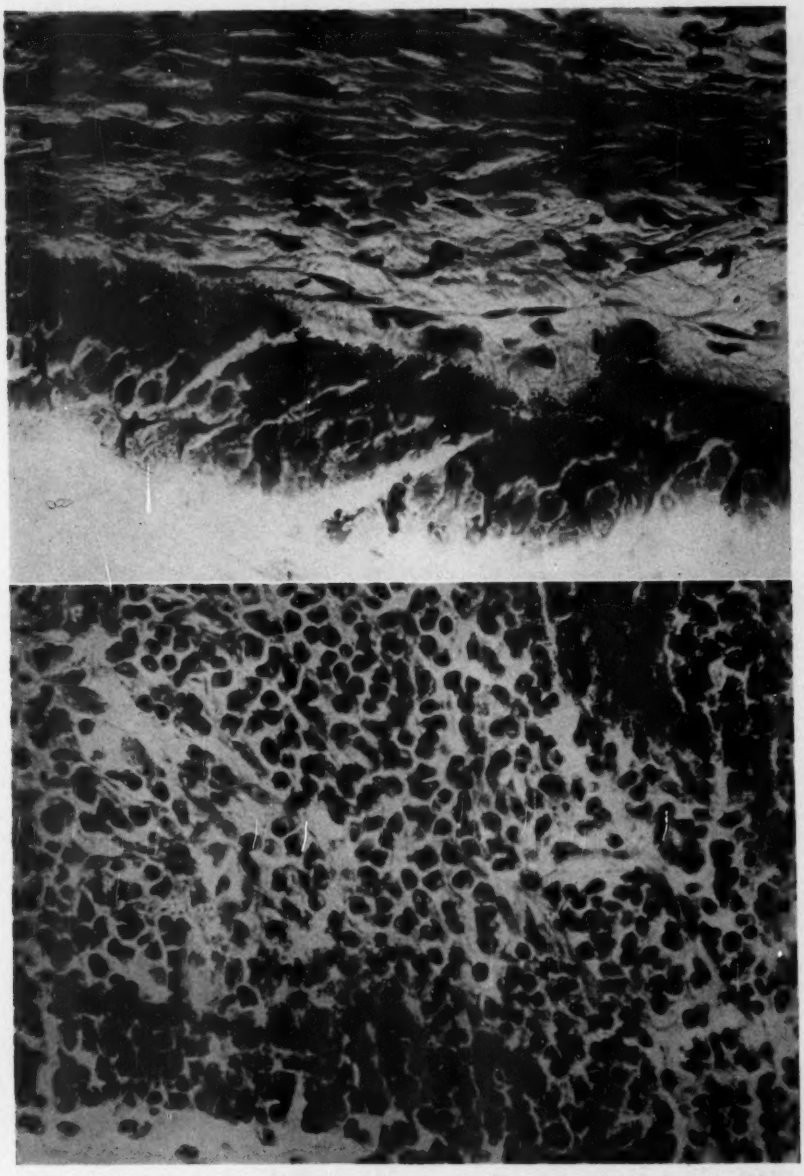

Fig. 4.—Ciliary body. Above, late treated eye, showing little or no cellular infiltration. Below, late control, showing heavy round cell infiltration (chiefly plasma cells), obscuring muscle fibers. There are derangement of pigmented epithelium and proliferation of unpigmented epithelial cells.

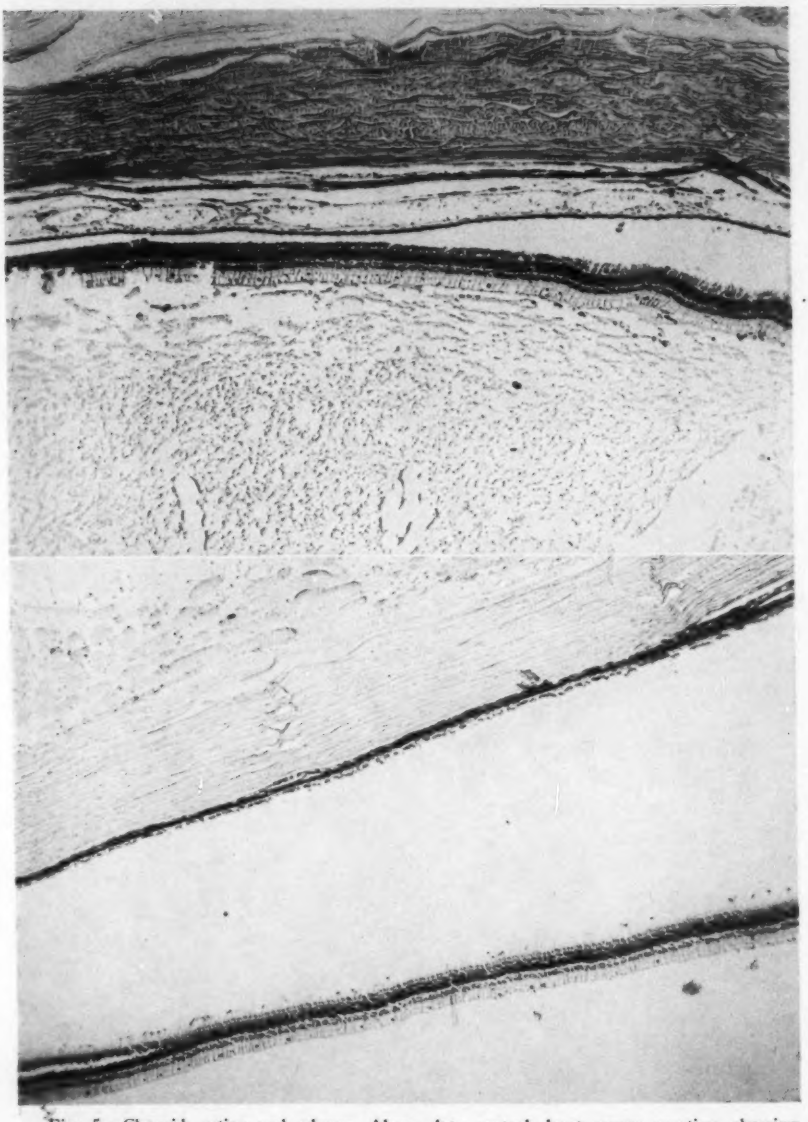

Fig. 5.—Choroid, retina and adnexa. Above, late control, least severe reaction, showing marked vitreous coagulum and cellular infiltration of choroid. Below, late treated, least severe reaction, showing normal appearance.

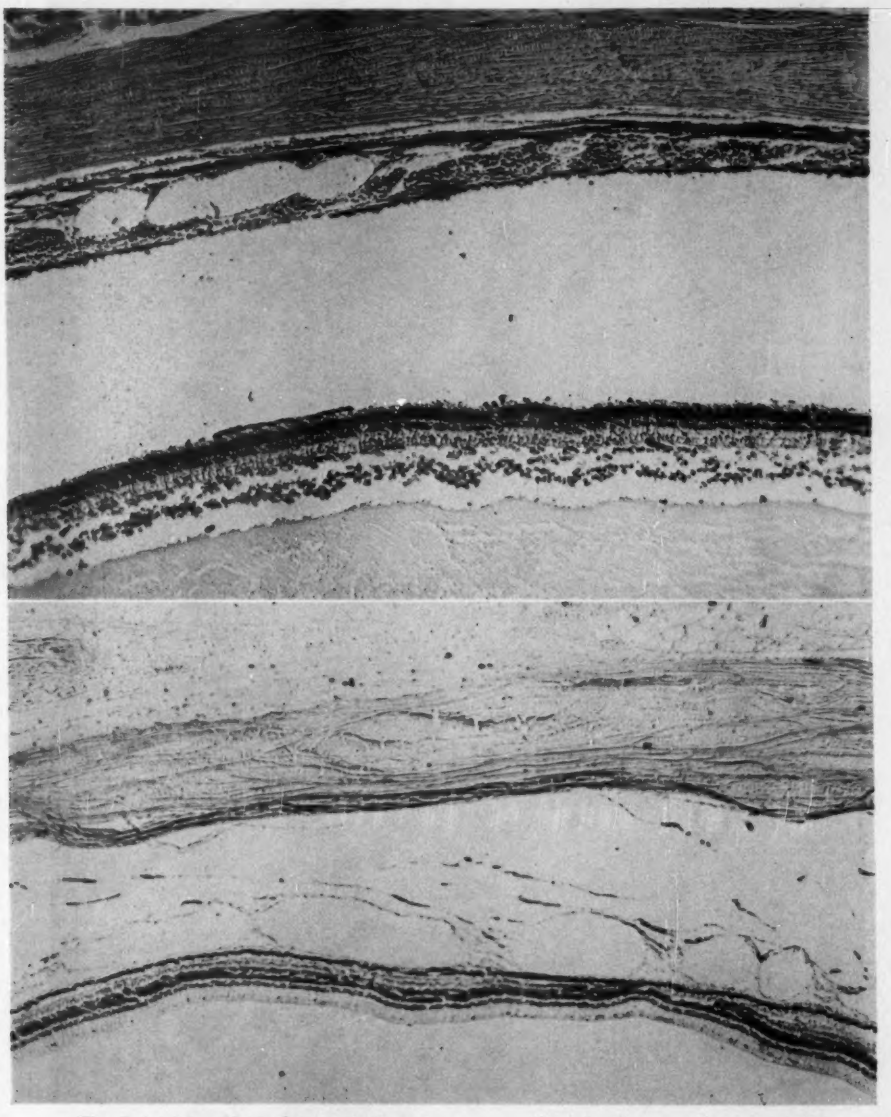

Fig. 5 (cont.).—Above, late control, most severe reaction, showing more intense reaction than that in the first photomicrograph (opposite page). Below, late treated, most severe reaction, showing slight cellular infiltration in choroid.

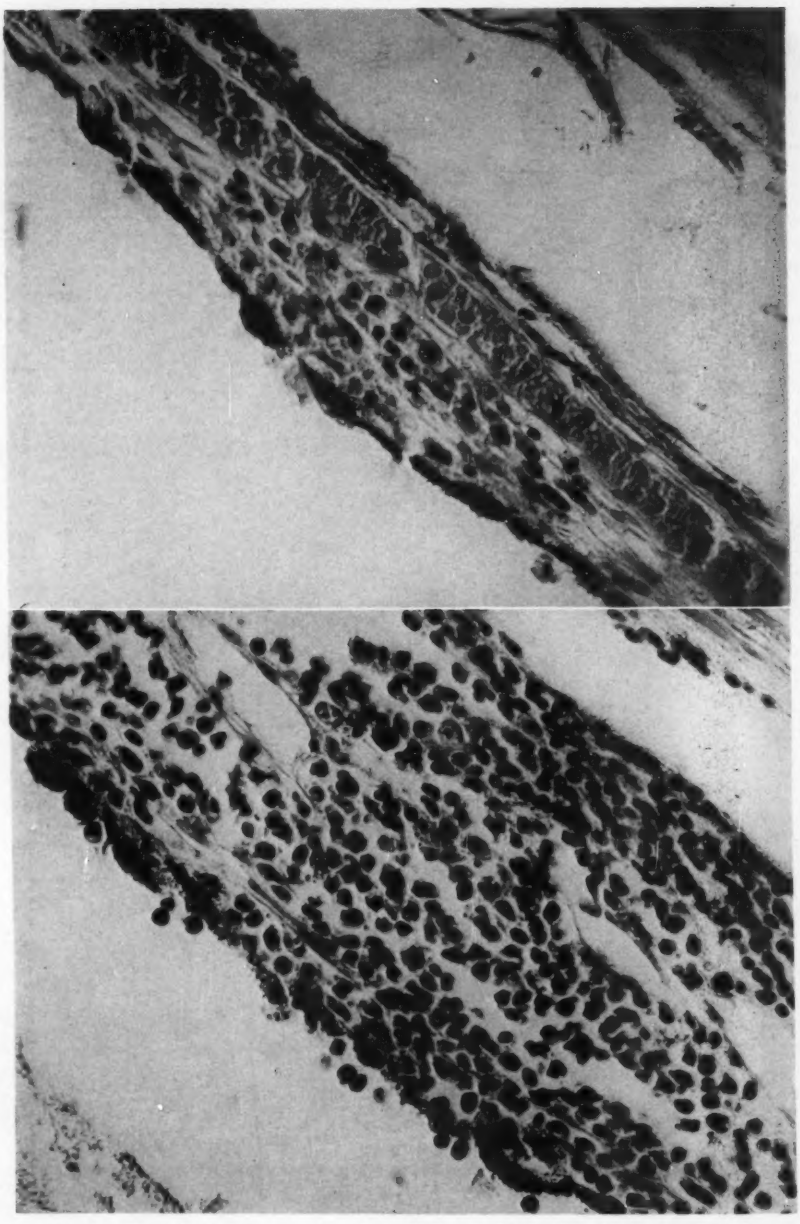

Fig. 6.—Choroid. Above, late control. A Dalen-Fuchs-like nodule is shown. Pigment epithelium is elevated by pale-staining cellular material. There is a small nodule of round cell infiltration in the adjacent choriocapillaris. Below, late control, showing intense cellular infiltration in choroid with mild elevation of pigment epithelium.

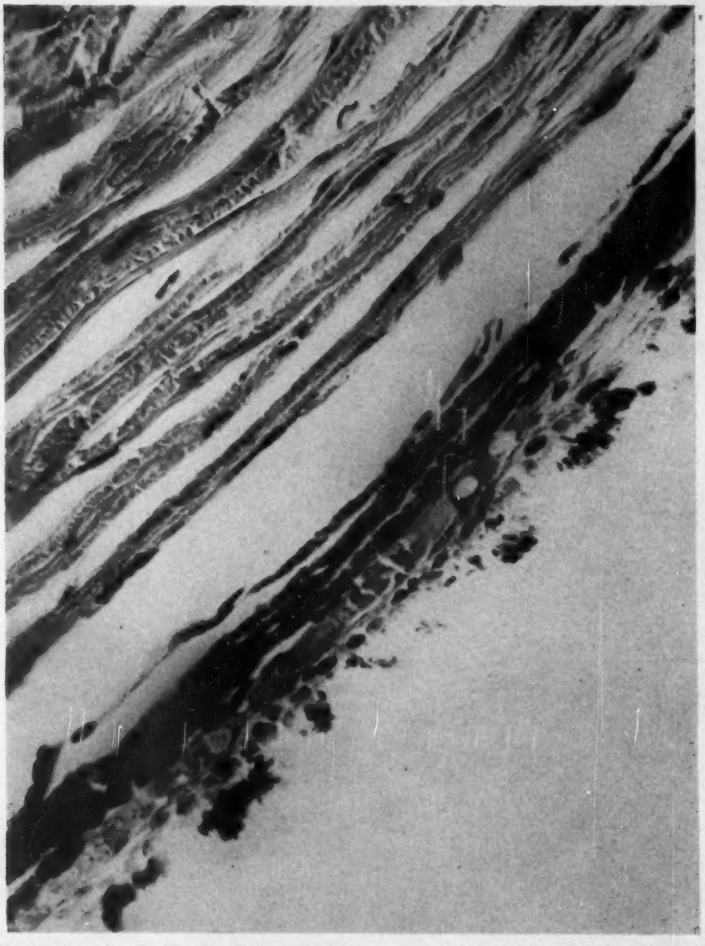

Fig. 6 (cont.).—Late treated eye, showing normal appearance except for disruption of pigment epithelium (artefact?).

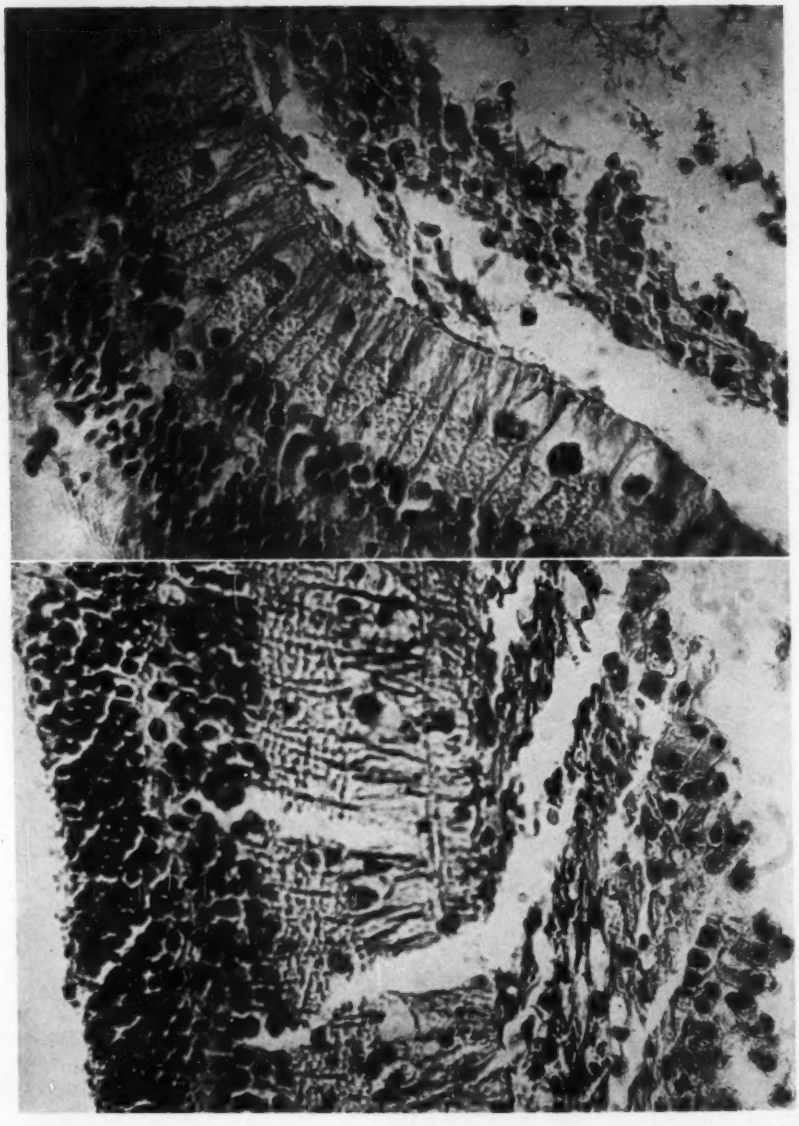

Fig. 7.—Retina. Above, late control, showing moderate proliferation of cells over retinal nerve fiber layer. Below, late control, showing marked cellular proliferation overlying retina.

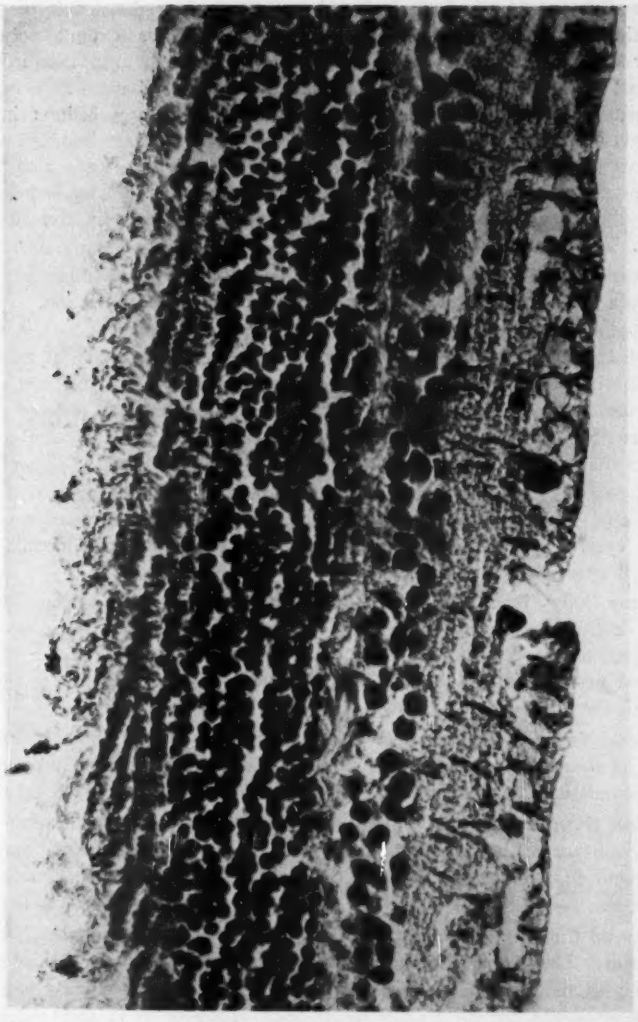

Fig. 7 (cont.).—Late treated eye, demonstrating absence of cellular proliferation overlying retina.

between the treated and the control eyes. The severest and the least severe reactions of the treated and of the control eyes are presented, illustrating some of the differences.

The early groups, both treated and untreated, showed uveal hyperemia and infiltration with immature round cells and, to a less extent, polymorphonuclear leukocytes. There was on the average a little more infiltration in the early untreated eyes. In the late groups, however, there was a striking difference between the treated eyes and the controls. There was slight, if any, cellular infiltration in the uvea of the treated eyes. The controls all contained large numbers of mature round cells, chiefly plasma cells and lymphocytes. There were also scattered areas of polymorphonuclear leukocytes and epithelioid cells. A detailed description of the difference between the treated and the control eyes in the late groups follows.

Circumcorneal Area: Cortisone-treated eyes showed considerably less fibrosis, hyperemia and round cell and polymorphonuclear leukocyte infiltration.

Anterior Chamber: The deposits on the anterior capsule of the lens observed by slit lamp microscopy before enucleation were seen on histological examination to contain inflammatory cells (chiefly immature round cells and polymorphonuclear leukocytes) and fibrinous material. The cortisone-treated eyes showed considerably less fibrin, inflammatory cells and protein coagulum throughout the anterior chamber than did the controls.

Iris (fig. 2): All the untreated eyes showed round cell infiltration (chiefly plasma cells), with relatively large numbers of mitotic figures, in contrast to the treated eyes. There were considerably more edema and hyperemia in the untreated eyes.

Ciliary Body (figs. 3 and 4): The ciliary body was the location of the most intense cellular reaction in the control eyes, including dense infiltration with round cells, small areas of epithelioid cells and a striking breakdown of the pigmented layer and proliferation of the ciliary epithelium. These changes were practically absent in the treated eyes.

Choroid (figs. 5 and 6): Quite striking was the paucity of Dalen-Fuchs-like nodules of round and epithelioid cells beneath the pigment epithelium of the retina and accumulations of round cells in the choroid of the treated eyes.

Retina (figs. 5 and 7): The striking proliferation and organization of cells over the surface of the retina following the intravitreal injection of horse serum was present in all four of the late controls. This was virtually absent in the treated eyes.

*Effect on Circulating Antibodies.*—The effect on the precipitin titer is recorded in the table. The average titer in the control rabbits on the twenty-third day was a little higher than that in the cortisone-treated rabbits, but, according to my data, this difference was not statistically significant. However, it is quite possible that if tests had been made at serum dilutions of 1:1,000,000 a significantly higher titer in the untreated animals might have been detected.

*Effect on Body Weight.*—There was a similar gain in weight of both treated and untreated rabbits.

## CONCLUSIONS

The daily administration of cortisone intramuscularly has a suppressing influence on most of the features of horse serum uveitis in rabbits. With doses of 25 mg. per kilogram of body weight per day, cortisone inhibits the following features of the reaction: (1) inflammatory cell infiltration and hyperemia of the circumcorneal area and uveal tract; (2) formation of plasmoid aqueous and cellular and fibrinous collections in the anterior chamber; (3) breakdown of the pigment border and proliferation of the ciliary epithelium; (4) Dalen-Fuchs-like nodules, and (5) vitreous coagulum and cells on the inner surface of the retina.

The data indicate that the precipitin titers of the treated rabbits were high despite the administration of cortisone, although perhaps lower than those of the controls. It appears that the beneficial effect of cortisone on the uveitis was more likely the result of inhibition of the inflammatory reaction itself than of the mere reduction in the systemic hypersensitivity to horse serum.

# USE OF ADRENOCORTICOTROPIC HORMONE AND CORTISONE IN OCULAR DISEASE

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E. L. WHITNEY, M.D.
DETROIT

OPHTHALMOLOGISTS have used nonspecific foreign protein therapy for years in the treatment of a variety of ocular lesions. As previously reported,[1] it was our belief that the benefit derived from this form of therapy could be attributed in part to the release of endogenous adrenocorticotropic hormone with an acceleration of mechanisms normally evoked in stress states. It has been shown by Sayers and Sayers [2] that both heat and killed typhoid organisms, among many factors, produce changes in the adrenal cortex of the experimental animal which are characteristic of the general response to stress. The same type of changes can be produced by the injection of adrenocorticotropic hormone. Talbot [3] and Venning [4] and their associates and others have shown a significant increase in the urinary excretion of 11-oxysteroids and 17-ketosteroids following a variety of stress states, such as trauma and surgical procedures. Forsham,[5] Mason,[6] and Sprague and associates [7] and others have demonstrated similar changes in the urinary excretion

From the Divisions of Ophthalmology, Metabolism and Gynaecology of the Henry Ford Hospital.

Read at the Ninety-Ninth Annual Session of the American Medical Association, Section of Ophthalmology, San Francisco, June 29, 1950.

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of the corticosteroids in human subjects receiving adrenocorticotropic hormone (ACTH). Selye[8] and Albright[9] have postulated that the response to stress is to a great extent elaborated through an increased production and release of the 11-oxycorticosteroids, and this has led to the wide use of cortisone (11-dehydro-17-hydroxycorticosterone), as well as ACTH in experimental treatment of many diseases.

On the premise that foreign protein therapy stimulates the release of endogenous ACTH, we attempted to determine whether or not exogenous ACTH or cortisone would achieve results comparable to those obtained with foreign protein therapy. In addition, attempts were made to determine the respective merits of ACTH and cortisone and, if possible, the selective application of each in ocular disease. The undesirable physiological side effect of pronounced salt and water retention has been observed during the administration of ACTH, and it was thought that this might be avoided by the sole administration of cortisone. ACTH stimulates all three zones of the adrenal cortex, whereas with cortisone the effects of the adrenal androgens and the principal electrolyte-controlling steroids are avoided. This might be desirable in patients with certain types of cardiovascular or renal disease, by whom prolonged ACTH might not be well tolerated.

It was postulated by us that cortisone would have physiological activity when applied directly to tissues involved in disease. This has been the subject of a previous report.[10] The significance of this form of therapy is obvious in that equivalent results might be obtained in selected cases without subjecting patients to the systemic physiological activity of cortisone and expenditure of the hormone.

This report covers the results obtained in the past six months with the experimental use of ACTH and cortisone. To date, 51 patients with inflammatory, degenerative, hereditary and other diseases of the eye have been studied, 37 of whom have received ACTH, and 14, cortisone.

## METHODS AND MATERIAL

*Clinical and Laboratory Studies.*—All patients receiving parenteral hormone therapy were admitted to the inpatient service of the Henry Ford Hospital, where complete physical examinations and detailed ophthalmologic studies were made. Ophthalmologic observations, which included visual field and tangent screen examinations, and biophotometric readings when indicated, were made immediately prior to the first administration of the drug and then at two, four and eight hour intervals. Thereafter, observations were made twice daily.

For each of the patients the following initial laboratory studies were made: a complete blood cell count; a direct eosinophil count, according to a modification of the method described by Forsham and associates[5]; blood serologic tests and routine urine analysis. Prior to and during administration of the hormone, all patients received a standard breakfast of determined carbohydrate content. Fasting and one hour postprandial blood sugar levels were determined on alternate days, a routine serving to indicate any changes in carbohydrate tolerance. In a

8. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. **6**:117-230, 1946.

9. Albright, F.: Cushing's Syndrome: Its Pathological Physiology, Its Relationship to the Adreno-Genital Syndrome, and Its Connection with the Problem of the Reaction of the Body to Injurious Agents ("Alarm reaction" of Selye), Harvey Lectures, 1942-1943, Baltimore, Williams & Wilkins Company, 1943.

10. Steffensen, E. H.; Olson, J. A.; Margulis, R. R.; Smith, R. W., and Whitney, E. L.: The Experimental Use of Cortisone in Inflammatory Eye Disease, Am. J. Ophth. **33**:1033-1040, 1950.

number of patients 24 hour specimens of urine were analyzed for sugar, while in others "spot" qualitative tests were made. As one measure of response, eosinophil counts were made prior to and four and 24 hours after the administration of the first dose of the drug. Thereafter the counts were taken at 24 and 48 hour intervals. As other indexes, white blood cell counts, differential counts and determinations of sedimentation rates were made at varying intervals. Blood pressures were charted twice daily. Weights were taken daily. In certain cases, serum electrolyte concentrations were determined, but the results of these and other studies are not pertinent to the present report.

*Treatment.*—ACTH [11] was administered intramuscularly at intervals of four or six hours in doses of 20 mg., except in cases 4 and 37, in which the initial doses were 10 and 5 mg. respectively. As the patient showed good clinical response or the cellular index (eosinophil and total leukocyte counts) revealed adrenocortical hyperfunction, the interval was increased to six or eight hours. Prior to cessation of treatment, the interval was increased to 12 hours. The maximum dose, in case 49, was 1,640 mg. (over a period of 21 days), and the longest period of treatment, in case 29, 23 days (1,310 mg.).

The same therapeutic program was used with cortisone,[12] starting with 50 mg. every four hours, except in case 40, in which the initial dose was 25 mg. every six hours. In this case it was found necessary to increase the dose to 50 mg. every six hours to obtain adequate laboratory response. As with ACTH, the interval gradually was lengthened to 6, 8 and then 12 hours when the change was justified by the clinical and laboratory findings. The maximum dose, in case 23, was 3,450 mg. given over a period of 17 days.

As indicated in table 2, certain patients with incomplete remissions or with recurrences of the inflammatory process in the anterior segment of the eye were subsequently treated with topical applications of cortisone. The topical preparation was made by diluting 1 volume of the saline suspension of cortisone with 4 volumes of isotonic sodium chloride solution. This was instilled in the eye every 30 to 60 minutes, the interval being increased as the patient responded.

It is emphasized that, except for the use of cycloplegic drugs in certain patients, no other definitive therapy was used during hormonal treatment.

## RESULTS OF LABORATORY STUDIES

The results of the laboratory studies and certain clinical observations pertinent to the present paper are presented in table 1.

*ACTH.*—With one exception (case 3), all patients receiving ACTH showed a striking reduction in circulating eosinophils. In case 2, that of a patient with suspected sarcoidosis, the reduction was greater than 50 per cent, but the absolute level was never below 220 cells per cubic millimeter. In case 3 the reduction in three days of treatment was only 40 per cent. In 3 cases (14, 20 and 41) the initial eosinophil counts were low, indicating high adrenal cortex activity. In these cases the ACTH-induced decrease in circulating eosinophils could not be used as a guide to therapy. In two of these (cases 20 and 41) the total leukocyte increase, however, indicated a good physiological response. The leukocytosis resulting from administration of ACTH was significant in 22 of the 31 cases in which it was adequately studied. This served as an additional measure of physiological response to the hormone and as a guide to dosage.

Control sedimentation rates were determined for 25 of the 37 patients receiving ACTH. The rate was significantly reduced in 14 of the 16 who showed an initial elevation. This result must be interpreted in the light of the duration of

11. The ACTH used in this study was obtained from Armour & Co., through the cooperation of Dr. John R. Mote, medical director, the Armour Laboratories, Chicago.

12. The cortisone used was the 11-dehydro-17-hydroxycorticosterone acetate (cortone®) of Merck & Company, Inc., Rahway, N. J. We received the cooperation of Dr. J. M. Carlisle, medical director of the Merck laboratories.

TABLE 1.—*Laboratory and Clinical Data* in Fifty-One Cases of Ocular Disease Before and After Hormonal Therapy*

| Case No. | Drug | Weight Lb. | | | Blood Pressure Deviations | Blood Sugar, Mg. | | | | Eosinophil | | White Blood Cell Count | | Sedimentation Rate | | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Fasting | | 1 Hr. P. C. | | | | | | | | |
| | | Init. | Rx. | Discharge | Sys./Dias. | Init. | Rx. | Init. | Rx. | Init. | Rx. | Init. | Rx. | Init. | Rx. | |
| 1 | ACTH | 129 | 130 | 129 | +15/+10 | 97 | 123 | ... | 177 | 50 | 0 | 7.3 | 9.6 | 51 | 29 | ..... |
| 2 | ACTH | 137 | 137 | 138 | +10/+20 | 94 | 106 | ... | 132 | 500 | 220 | 6.9 | 12.8 | 23 | 13 | ..... |
| 3 | ACTH | 151 | 150 | 147 | 0/—10 | 85 | 113 | 120 | 129 | 120 | 74 | 4.3 | 7.3 | 30 | 26 | ..... |
| 4 | ACTH | 209 | 202 | 205 | 0/—10 | 113 | 116 | 120 | 136 | 300 | 0 | 7.9 | 11.2 | 26 | 5 | ..... |
| 5 | ACTH | 114 | 112 | 112 | +15/+10 | 97 | 94 | 129 | 120 | 114 | 13 | 7.6 | 10.7 | .. | 13 | ..... |
| 6 | ACTH | 162 | 164 | 165 | +15/+5 | 87 | 120 | ... | 188 | 329 | 24 | 11.4 | 14.4 | .. | 32 | ..... |
| 7 | ACTH | 132 | 137 | 130 | —10/0 | 95 | 123 | 143 | 167 | 109 | 29 | 9.7 | 20.0 | 45 | 26 | ..... |
| 8 | Cortisone | 131 | 133 | 131 | +20/+20 | 100 | ... | ... | ... | 250 | 10 | 7.4 | .... | .. | .. | ..... |
| 9 | Cortisone | 170 | 168 | 170 | —20/—5 | 106 | ... | 146 | ... | 144 | 32 | 6.5 | .... | .. | .. | ..... |
| 10 | Cortisone | 201 | 200 | 200 | —35/—12 | 87 | 87 | ... | 123 | 77 | 13 | 10.9 | 10.2 | .. | 45 | ..... |
| 11 | Cortisone | 180 | 178 | 180 | 0/0 | 103 | 120 | 100 | 139 | 80 | ... | 6.3 | 12.5 | 0 | 27 | ..... |
| 12 | Cortisone | 140 | 139 | 140 | +15/0 | 106 | 97 | 146 | 149 | 0 | 10 | 13.3 | .... | 29 | 33 | ..... |
| 13 | Cortisone | 166 | 168 | 162 | —15/0 | ... | 103 | ... | 129 | 56 | 32 | 16.4 | 15.8 | 37 | 16 | ..... |
| 14 | ACTH | 149 | 154 | 151 | 0/+10 | ... | ... | ... | ... | 16 | 32 | 11.9 | .... | 8 | .. | ..... |
| 15 | ACTH | 124 | 133 | 122 | +10/+15 | 113 | 109 | 100 | 188 | 206 | 5 | 6.0 | 14.0 | 10 | 0 | Glycosuria 6 Gm./24 hr.; leg edema ++ |
| 16 | ACTH | 117 | 123 | 122 | +10/+10 | 100 | 113 | 97 | 156 | 54 | 0 | 7.2 | 17.1 | 19 | 7 | ..... |
| 17 | ACTH | 148 | 153 | 148 | +30/+10 | 80 | 122 | ... | 129 | 123 | 0 | 10 | 19 | 14 | 0 | ..... |
| 18 | Cortisone | 88 | 91 | 88 | +25/+10 | 97 | 94 | ... | 123 | 290 | 8 | 6.7 | 13.1 | 10 | 34 | ..... |
| 19 | ACTH | 166 | 168 | 168 | 0/—10 | 65 | 94 | ... | 123 | 192 | 16 | 5.7 | 11.9 | 13 | 5 | Glycosuria, transitory |
| 20 | ACTH | 162 | 162 | 157 | 0/0 | 97 | 120 | 166 | 146 | 32 | 16 | 6.3 | 15.8 | .. | 3 | Glycosuria, transitory to 8 Gm./24 hr. |
| 21 | Cortisone | 205 | 203 | 203 | 0/0 | 106 | 80 | 100 | ... | 176 | 0 | 10.9 | .... | .. | .. | ..... |
| 22 | ACTH | 176 | 177 | 172 | —5/0 | 109 | 123 | 136 | 154 | 153 | 0 | 6.0 | 12.2 | 5 | 7 | Glycosuria, transitory |
| 23 | Cortisone | 109 | 113 | 112 | 0/0 | 94 | 123 | 158 | 158 | 254 | 82 | 6.8 | 14.7 | 14 | 11 | ..... |
| 24 | ACTH | 192 | 194 | 186 | +30/+30 | 70 | 103 | ... | 103 | 68 | 0 | 4.0 | .... | 5 | 8 | ..... |
| 25 | Cortisone | 120 | 128 | 124 | 0/—20 | 97 | 126 | 97 | 136 | 34 | 19 | 8.6 | 22.5 | .. | .. | ..... |
| 26 | Cortisone | 101 | 94 | 99 | +20/+10 | ... | 116 | 85 | 120 | 205 | 7 | 5.0 | 14.5 | 1 | 21 | ..... |
| 27 | (See case 3) | | | | | | | | | | | | | | | |
| 28 | ACTH | 105 | 111 | 106 | +10/0 | 97 | 123 | 139 | 149 | 147 | 0 | 6.0 | 9.8 | 5 | 0 | ..... |
| 29 | ACTH | 113 | 121 | 118 | +10/+10 | 85 | 106 | 89 | 167 | 33 | 0 | 6.7 | 8.1 | .. | .. | Glycosuria, 3 Gm./24 hr. |
| 30 | ACTH | 99 | 105 | 97 | 0/0 | 70 | 113 | ... | 163 | 48 | 0 | 6.2 | 10.5 | 30 | 20 | ..... |
| 31 | ACTH | 120 | 125 | 122 | —20/0 | 108 | 132 | 146 | 188 | 251 | 37 | 7.9 | 14.4 | 25 | 7 | ..... |
| 32 | ACTH | 154 | 161 | 159 | +15/0 | 97 | 97 | 113 | 146 | 48 | 0 | 5.2 | 16.4 | .. | 3 | Glycosuria, transitory |
| 33 | ACTH | 155 | 162 | 155 | +20/+10 | 100 | 103 | 92 | 149 | ... | 3 | 8.6 | 15.0 | .. | 0 | ..... |
| 34 | ACTH | 126 | 128 | 128 | 0/0 | ... | 120 | ... | 139 | 112 | 0 | 6.6 | 11.4 | 6 | 4 | ..... |
| 35 | ACTH | 150 | 153 | 150 | 0/0 | 94 | 120 | ... | 188 | 96 | 0 | 8.3 | 9.5 | 3 | 3 | ..... |
| 36 | ACTH | 132 | 135 | 134 | —40/—25 | 85 | 126 | ... | 188 | 174 | 10 | 12.4 | 14.8 | .. | .. | ..... |
| 37 | ACTH | 51 | 51 | 50 | +10/+15 | 70 | 100 | 126 | 92 | 55 | 19 | 6.1 | 7.3 | .. | 12 | ..... |
| 38 | ACTH | 128 | 142 | 131 | +15/0 | 85 | 116 | 116 | 149 | ... | 0 | 8.0 | 21.5 | .. | .. | ..... |
| 39 | ACTH | 179 | 179 | 187 | +30/+20 | 92 | 89 | ... | 142 | 283 | 71 | 7.9 | 14.7 | 10 | 0 | ..... |
| 40 | Cortisone | 78 | 82 | 80 | +10/+10 | 94 | 100 | ... | ... | 67 | 10 | 3.9 | 17.8 | 25 | 26 | ..... |
| 41 | ACTH | 141 | 146 | 138 | +30/+20 | 129 | 167 | 100 | 163 | 8 | 2 | 7.7 | 12.6 | 20 | 3 | ..... |
| 42 | ACTH | 213 | 217 | 211 | 0/0 | 87 | 103 | 100 | 183 | 88 | 16 | 8.1 | .... | .. | .. | ..... |
| 43 | ACTH | 106 | 111 | 108 | Marked fluctuations | 226 | 288 | ... | ... | 405 | 10 | 5.7 | .... | 19 | 02 | Insulin requirements † |
| 44 | ACTH | 162 | 167 | 156 | 0/0 | 100 | 120 | 123 | 183 | 196 | 0 | 8.0 | 17.8 | 28 | 0 | Glycosuria, transitory |
| 45 | ACTH | 170 | 175 | 165 | —10/0 | 123 | 143 | 156 | 177 | 325 | 75 | 8.2 | 10.6 | 30 | 28 | Glycosuria, mild |
| 46 | ACTH and cortisone | 116 | 121 | 117 | +10/0 | 97 | 100 | ... | 113 | 264 | 3 | 8.8 | 11.7 | .. | 06 | ++++ Kahn reaction |
| 47 | ACTH | 194 | 195 | 190 | +10/+20 | 80 | 103 | 97 | 116 | 231 | 0 | 4.3 | 16.1 | .. | .. | Glycosuria, transitory; 1+ edema |
| 48 | ACTH | 166 | 167 | 165 | 0/0 | 100 | 116 | 120 | 173 | 65 | 3 | 9.4 | 19.6 | 30 | 1 | ..... |
| 49 | ACTH | 149 | 157 | 148 | +20/+10 | 109 | 123 | ... | 200 | 330 | 0 | .... | .... | 25 | 5 | ..... |
| 50 | ACTH | 172 | 175 | 169 | 0/0 | 89 | 132 | 126 | 156 | 179 | 7 | 8.5 | 17.4 | 32 | 24 | ..... |
| 51 | Cortisone | ... | 119 | ... | ..... | ... | 154 | ... | 186 | ... | 13 | .... | 10.3 | .. | 9 | Treatment only 24 hr. |

* In this table "Init." stands for "Initial"; "Rx." for "Treatment," and "1 Hr. P. C." "1 Hour Postprandial."
† Insulin requirements: protamine zinc insulin 15 u. to regular insulin 80 u., with up to 26 Gm. glucose in urine.

treatment, which in many cases was relatively brief, and little emphasis was placed on the changes.

The alterations in carbohydrate metabolism as reflected in fasting and postprandial glucose concentrations likewise were viewed with reservation and served only to indicate when great reductions in carbohydrate tolerance had developed. In 22 of the patients receiving ACTH there appeared to be some reduction in carbohydrate tolerance, and in 10 of these (cases 15, 16, 29, 31, 33, 41, 42, 43, 44 and 49) it appeared to be a significant but transient change. One patient (case 43) had diabetes which was controlled on a regimen of 15 units of protamine zinc insulin, and while receiving ACTH she required 80 units of regular insulin, with instability of control of the diabetes. Tests for urinary glucose, which were made on a number of patients receiving ACTH, gave positive results in eight patients, excluding the diabetic patient (case 43). A maximum of 8 Gm. per 24 hours was found in case 20, while in cases 15 and 29 the urinary excretion was 6 and 3 Gm., respectively. The glycosuria cannot be related, necessarily, to the changes in blood sugar, since the presence of the former was not determined routinely.

*Cortisone.*—In patients receiving cortisone the change in the circulating eosinophils was a less reliable index of adequate dosage, in contrast to the patients receiving ACTH. In some patients the drop was immediate and greater than 50 per cent, occurring as early as the second hour, while in others the fall was gradual, over several days. In all but one patient (case 13) a marked reduction was eventually achieved. As with ACTH, leukocytosis was usually observed and served as a useful guide to therapy.

Changes in sedimentation rates were studied adequately in only seven of the patients receiving cortisone. Of three initially high rates (cases 12, 13 and 40), only one (case 13) was brought to normal. For three patients with normal initial values (cases 11, 18 and 26) the sedimentation rate became significantly elevated during treatment.

A slight reduction in carbohydrate tolerance was seen in only one (case 25) of eight patients adequately studied, and glycosuria was not observed in any.

## CLINICAL RESULTS

### Inflammatory Lesions

*Acute Iridocyclitis.*—The largest group of cases studied in this series was that of the acute inflammatory reactions in the anterior uveal tract. In each of the 13 patients the condition was considered severe, with nine failing to respond to previous treatment, which included cycloplegia, foreign protein therapy and use of salicylates, local heat and antibiotics.

As shown in table 2, seven of the patients were treated with ACTH and six with cortisone. The results of treatment with the two drugs were comparable. Subjectively, the relief of pain and photophobia in these 13 patients was rapid. Except for patient 13, these symptoms were gone at the end of four hours after the first parenteral injection. Patient 13 experienced complete relief of pain and photophobia at the end of 24 hours.

In nine of the 13 patients the anterior chamber showed a moderate to heavy fibrinous exudate while in two it contained a smaller amount and in the remaining two it was free from gross fibrin. Hemorrhage was present in the anterior chamber

of three patients. Within 45 minutes to two hours, the smaller amounts of fibrin disappeared from the anterior chamber, while the larger amounts required as much as 24 hours for clearance. In a very severe case (case 4) with superimposed hyphema, the free fibrin was not absorbed until after 30 hours of treatment.

Flare and cells in the anterior chamber disappeared with proportionate rapidity. In no eye was flare present after 48 hours; in three patients the anterior chamber was free of cells within three days, while in the other 10 patients it cleared in four to 12 days. One patient (case 7), who had been under ambulatory treatment for two months, with gradual increase in severity of the iridocyclitis, had persisting iridocyclitis after 14 days of hormone therapy. There was no response after an additional 10 days of topical applications of cortisone. The response of the four patients with secondary glaucoma was striking. Two patients, one of whom (case 4) was treated with ACTH and the other (case 11) with cortisone, showed a reduction of intraocular pressure from 48 mm. of mercury (Schiøtz) to a normal of 23 mm. within four hours. The other two patients (cases 5 and 12) with initial intraocular tensions of 35 and 48 mm., responded in 44 hours and four days, respectively.

Six of the seven patients treated with ACTH have been under observation for four to six months, and three of the group treated with cortisone, for at least two months. The rest of the two groups has been under observation for four to seven weeks.

In the group treated with ACTH there has been but one recurrence (case 1), and this was after the eye had been entirely clear for two months. The patient was placed under cortisone therapy (case 8) and responded rapidly. She was free of any activity for 17 days, after which there was evidence of a mild relapse, which was controlled in 24 hours with the topical application of cortisone. This patient had no further recurrence during six weeks of observation.

Two additional patients receiving cortisone had mild recurrences of their symptoms and signs—patient 9 after 14 days and patient 10 after four weeks. Both responded quickly to topical application of cortisone, and both have now been free of activity for two months.

*Acute Choroiditis.*—The visible response of acute choroiditis to treatment with ACTH and cortisone was perhaps less dramatic than that of the acute inflammations of the anterior segment. The lesions, however, became inactive, and repair processes started sooner than in similar conditions treated with foreign protein therapy. In three of the five patients the lesions were recurrent. The macular area was not involved in any of this group. All patients noted blurred vision as their only presenting symptom. The onset varied from four days to three months prior to hormone therapy, and three patients had no previous treatment. One patient (case 15) treated with ACTH had received, over a previous three months, intensive foreign protein therapy, and antibiotic and vasodilator medication, without benefit. In case 18 similar therapy had also been given, without improvement, three weeks before cortisone was administered. Visual acuity was reduced to 20/44 in three patients, to 20/52 in the fourth patient and to 20/137 in the fifth patient, who had a very large lesion close to the disk. In each of the five eyes the lesion was covered with a heavy white exudate, surrounded by varying amounts of retinal edema. In two eyes the lesion was sufficiently near the nerve head to

TABLE 2.—*Data on Treatment of Ocular Diseases with ACTH and Cortisone*

| Case No. | Age, Yr. | Sex | Diagnosis | Drug | Total Dose, Mg. | Duration of Treatment, Days | Results | Time Required, Days | Follow-Up Status | Observation Period | Complications |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Inflammatory Diseases | | | | |
| 1 | 50 | F | Acute iridocyclitis | ACTH | 195 | 3 | Complete remission | 3 | Recurrence | 2 mo. | None |
| 2 | 34 | F | Acute iridocyclitis | ACTH | 185 | 3 | Complete remission | 3 | No recurrence | 6 mo. | None |
| 3 | 55 | M | Acute iridocyclitis | ACTH | 210 | 3 | Complete remission | 3 | No recurrence | 5 mo. | None |
| 4 | 61 | M | Acute iridocyclitis | ACTH | 630 | 14 | Complete remission | 17 | No recurrence | 5 mo. | None |
| 5 | 41 | F | Acute iridocyclitis | ACTH | 220 | 4 | Complete remission | 3 | No recurrence | 4 mo. | None |
| 6 | 50 | F | Acute iridocyclitis | ACTH | 225 | 3 | Complete remission | 2 | No recurrence | 5 mo. | None |
| 7 | 50 | F | Acute iridocyclitis | ACTH | 1,080 | 14 | Incomplete remission | .. | Persistent iridocyclitis, uncontrolled by topical use of cortisone | 1 wk. | None |
| 8 | 50 | F | Acute iridocyclitis | Cortisone | 900 | 3 | Complete remission | 3 | Recurrence, controlled by topical use of cortisone; no recurrence | 17 days<br>24 hr.<br>3 mo. | None |
| 9 | 66 | F | Acute iridocyclitis | Cortisone | 425 | 2 | Complete remission | 2 | Recurrence controlled by topical use of cortisone; no recurrence | 14 days<br>4 days<br>2 mo. | None |
| 10 | 35 | F | Acute iridocyclitis | Cortisone | 1,350 | 6 | Complete remission | 5 | Recurrence controlled by topical use of cortisone; no recurrence | 1 mo.<br>4 days<br>2 mo. | None |
| 11 | 39 | M | Acute iridocyclitis | Cortisone | 775 | 5 | Complete remission | 3 | No recurrence | 2 mo. | None |
| 12 | 47 | F | Acute iridocyclitis | Cortisone | 1,200 | 6 | Complete remission | 4 | No recurrence | 6 wk. | None |
| 13 | 54 | M | Acute iridocyclitis | Cortisone | 1,300 | 8 | Complete remission | 8 | No recurrence | 4 wk. | None |
| 14 | 38 | M | Acute chorioretinitis | ACTH | 600 | 10 | Remission continuing | .. | No recurrence | 3 mo. | None |
| 15 | 23 | F | Acute chorioretinitis | ACTH | 740 | 10 | Complete remission | 12 | No recurrence | 2 mo. | None |
| 16 | 25 | F | Acute chorioretinitis (Jensen) | ACTH | 1,160 | 15 | Remission continuing | .. | No recurrence | 6 wk. | Mild acne |
| 17 | 41 | F | Acute chorioretinitis | ACTH | 1,040 | 14 | Remission continuing | .. | No recurrence | 6 wk. | Mild acne |
| 18 | 28 | F | Acute chorioretinitis | Cortisone | 2,850 | 14 | Remission continuing | .. | No recurrence | 2 mo. | None |
| 19 | 57 | M | Retinitis centralis | ACTH | 330 | 7 | Complete remission | 4 hr. | No recurrence | 5 mo. | None |
| 20 | 33 | M | Retinitis centralis | ACTH | 920 | 12 | Complete remission | 8 | No recurrence | 2 mo. | None |
| 21 | 48 | M | Retinitis centralis | Cortisone | 1,150 | 5 | Complete remission | 4 | No recurrence | 3 mo. | None |
| 22 | 50 | M | Acute diffuse uveitis | ACTH | 680 | 12 | Incomplete remission | .. | Remission completed with topical use of cortisone | ..... | None |
| 23 | 29 | F | Acute diffuse uveitis | Cortisone | 3,450 | 17 | Incomplete remission | .. | Remission completed with topical use of cortisone | ..... | None |
| 24 | 47 | M | Acute optic neuritis | ACTH | 1,010 | 16 | Incomplete remission | .. | Recurrence slight | 3 mo. | None |
| 25 | 18 | F | Acute optic neuritis | Cortisone | 2,600 | 12 | Complete remission | 12 | No recurrence | 6 wk. | None |
| 26 | 13 | M | Optic neuriti. with neuroretinitis | Cortisone | 1,650 | 9 | Complete remission | 7 | No recurrence | 6 wk. | None |
| 27 (See case 3) | 55 | M | Chronic granulomatous iridocyclitis | ACTH | 210 | 3 | Incomplete remission | .. | Recurrence | 5 wk. | None |
| 28 | 47 | F | Chronic granulomatous iridocyclitis | ACTH | 530 | 8 | Complete remission | 6 | Recurrence | 10 wk. | None |
| 29 | 32 | F | Chronic granulomatous iridocyclitis | ACTH | 1,310 | 23 | Incomplete remission | .. | Recurrence | 1 wk. | None |
| 30 | 49 | M | Chronic granulomatous iridocyclitis | ACTH | 800 | 9 | Incomplete remission | .. | Recurrence | 1 wk. | None |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 31 | 50 | F | Chronic granulomatous iridocyclitis | ACTH | 540 | 9 | Complete remission | 17 | Recurrence | 4 wk. | None |
| 32 | 35 | F | Central chorioretinitis | ACTH | 1,000 | 15 | Incomplete remission | .. | Recurrence | 1 wk. | None |
| 33 | 38 | M | Central chorioretinitis | ACTH | 1,050 | 15 | Very little response | .. | Recurrence | 4 days | None |
| 34 | 47 | M | Chronic exudative posterior uveitis | ACTH | 780 | 9 | No response | .. | ..... | ..... | None |
| | | | | | | | Degenerative Diseases | | | | |
| 35 | 60 | M | Disciform degeneration of macula (Kuhnt-Junius disease) | ACTH | 260 | 4 | No response | .. | Disease process continuing | 3 mo. | None |
| 36 | 44 | M | Angioid streaks and pseudoxanthoma elasticum | ACTH | 940 | 11 | No response | .. | No change | 3 wk. | None |
| 37 | 6 | M | Bilateral pigmented macular degeneration | ACTH | 140 | 7 | No response | .. | Progressive pigmented changes | 3 mo. | None |
| 38 | 22 | M | Pigmented retinitis with secondary glaucoma | ACTH | 1,120 | 13 | No response | .. | No change | 2 wk. | Mild acne |
| | | | | | | | Hereditary Diseases | | | | |
| 39 | 42 | M | Advanced retinitis pigmentosa | ACTH | 340 | 6 | Could not evaluate | .. | ..... | ..... | None |
| 40 | 9 | M | Early retinitis pigmentosa | Cortisone | 1,800 | 14 | Improved | 12 | Improvement maintained | 10 wk. | None |
| | | | | | | | Miscellaneous Diseases | | | | |
| 41 | 60 | F | Herpes zoster ophthalmicus | ACTH | 740 | 11 | Complete remission | 2 | Slight recurrence of iritis controlled by topical use of cortisone | 1 wk.<br>4 days | None |
| 42 | 65 | M | Severe rosacea keratoconjunctivitis | ACTH | 1,080 | 10 | Complete remission | 3 | Slight recurrence controlled by topical use of cortisone | 3 days<br>1 day | Mild acne |
| 43 | 66 | F | Vitreous abscess | ACTH | 520 | 7 | Incomplete remission | .. | Recurrence | 4 days | None |
| 44 | 62 | M | Anterior granulomatous scleritis | ACTH | 695 | 15 | Incomplete remission | .. | Recurrence controlled with continued topical use of cortisone | 1 wk. | None |
| 45 | 63 | F | Severe postoperative keratitis with iridocyclitis | ACTH | 510 | 14 | Incomplete remission | .. | Recurrence controlled with continuing topical use of cortisone | 1 wk. | Auricular fibrillation |
| 46 | 15 | F | Atypical congenital syphilitic keratitis | ACTH;<br>Cortisone | 240<br>2,450 | 3<br>11 | Marked improvement | .. | Remission continuing with topical use of cortisone | 6 wk. | Amenorrhea, 2 mo. only |
| 47 | 19 | M | Severe vernal conjunctivitis | ACTH | 1,340 | 16 | Marked improvement | .. | Recurrence | 2 wk. | Slight acne; epistaxis |
| 48 | 46 | M | Transitional cell carcinoma of limbus | ACTH | 670 | 8 | Temporarily arrested | .. | Recurrence of activity | 12 days | None |
| 49 | 51 | M | Optic atrophy due to optic neuritis | ACTH | 1,040 | 21 | No response | .. | ..... | ..... | None |
| 50 | 56 | F | Bilateral chronic simple glaucoma | ACTH | 110 | 1 | No response | .. | ..... | ..... | None |
| 51 | 61 | F | Acute congestive glaucoma—aphakia | Cortisone | 300 | 1½ | No response | .. | ..... | ..... | None |

cause pronounced papilledema, and in one of these eyes a typical picture of juxtapapillary choroiditis of Jensen was presented. In all cases the vitreous was hazy and filled with cells and the number of cells in the anterior chamber was graded 1+ to 2+. In three of the patients the keratic precipitates were graded 2+, and in another the endothelial surface of the cornea was heavily covered with small keratic precipitates, fibrin and cellular debris.

Response to therapy was first noted by the disappearance of cells from the anterior chamber as early as two days and not later than eight days. The four patients with keratic precipitates were free of these at the conclusion of treatment. The edema surrounding the lesions subsided gradually and in all was gone before treatment was concluded. Because of the vitreous haze, the area of edema was best demonstrated by daily tangent screen examinations. The scotomas gradually diminished, appearing to be representative of the changes in the lesion itself. The vitreous haze and the exudate over the lesion gradually diminished, so that at the

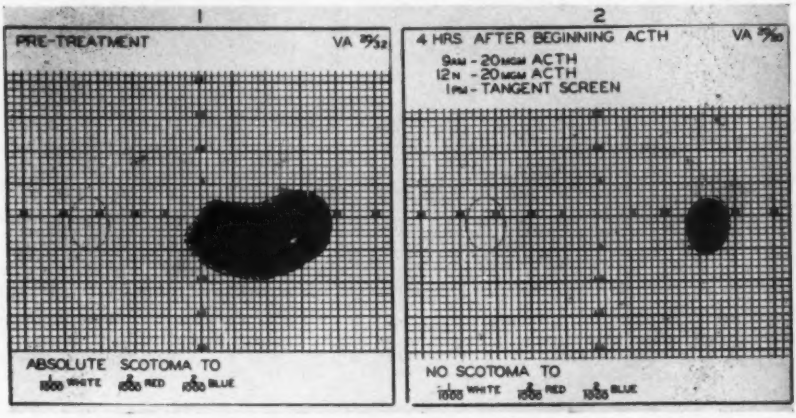


Fig. 1 (case 19).—Retinitis centralis of the right eye in a man aged 57. Tangent screen fields show the rapid disappearance of the scotoma and improved visual acuity four hours after the initial dose of ACTH. The disease has not recurred in five months.

conclusion of treatment vision was 20/32 or better in each of the treated eyes. All the patients have been followed six to 12 weeks after withdrawal of therapy, and their eyes have continued to show clearing.

*Retinitis Centralis.*—Although the etiology of this lesion is open to question, it was believed that the condition in the present cases was of inflammatory, rather than angiospastic origin.

Case 19.—The patient was the only one of this group who had had a previous episode, and this had been treated intensively with foreign protein, vasodilators and thiamine chloride, with the elimination of a central scotoma and restoration of visual acuity to 20/20 within two to three weeks. At the time of his admission for ACTH therapy there had been recurrence of blurred vision in the same eye, of two days' duration. Examination of the fundus revealed a small area of depigmentation adjacent to the macula with a surrounding area of mild edema and hyperemia of about 1 disk diameter. Tangent screen determinations (fig. 1) showed the original scotoma and its rapid response to treatment. Edema and hyperemia subsided entirely during treatment, but the small area of depigmentation has remained unchanged.

CASE 20.—A very small area of retinitis centralis with minimal edema was superimposed on a macula of definite granular appearance. The granular appearance was apparent also in the opposite eye. Although the patient complained that the vision was blurred, his vision was 20/20, and the tangent screen test revealed only a 2 degree absolute scotoma for 3/1000 blue. Four hours after administration of the original 20 mg. dose of ACTH there was a relative scotoma for 3/1000 blue at the fixation point only, and subjectively the patient showed improvement. This fine relative scotoma persisted through the fifth day, after which it disappeared, to recur vaguely on the seventh and eighth days. Since the eighth day tangent screen examinations have shown a normal field. The minimal edema and hyperemia gradually diminished and disappeared on the eighth day, but in all other respects both fundi remained the same.

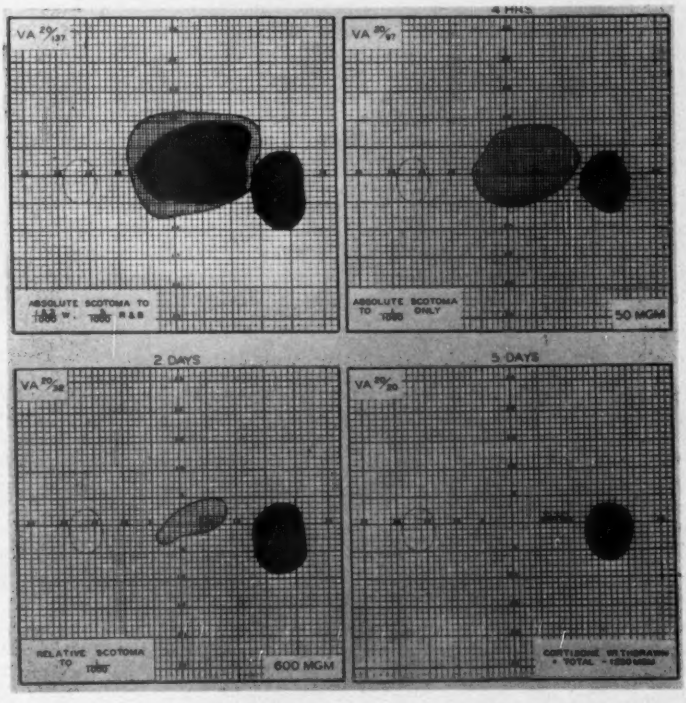


Fig. 2 (case 21).—Retinitis centralis of the right eye of three weeks' duration. Tangent screen fields show the rapid disappearance of the central scotoma and improvement in visual acuity with five days of cortisone therapy. There has been no recurrence in two months. Cortisone was given every four hours from the first to the third day, inclusive, and every six hours on the fourth and fifth days.

CASE 21.—The patient complained of diminution of vision for a three week period prior to his admission to the hospital. Findings in the fundus were identical with those in case 19. Figure 2 illustrates the original scotoma and the resultant improvement under treatment. Changes in the fundus were comparable in every way to those in case 19.

These patients have been followed five, two and three months, respectively, without evidence of recurrence.

*Acute Diffuse Uveitis.*—Two patients were studied in this group.

CASE 22.—The patient had previously lost his left eye, after prolonged, extensive uveitis. The present episode began four months before his admission to the hospital, with clouding of the vitreous and blurring of vision without localizing choroidal lesions. Cycloplegia, foreign protein therapy and use of antibiotics did not alter the course of the increasing inflammatory process. At the time therapy was started both the anterior and the posterior uveal tract were involved.

CASE 23.—The patient had severe bilateral involvement of one month's duration. The referring physician had hospitalized her for intensive foreign protein and antibiotic therapy, to which she had responded fairly well, but she had a relapse three days after leaving the hospital. The same therapy was continued at home, but the condition became progressively worse. On her admission, neither fundus could be seen because of the intense cellular infiltration of the vitreous and a 2 + aqueous flare and 3 + cellular count in the aqueous of each eye. Both eyes showed pronounced wrinkling of Descemet's membrane and intense circumcorneal injection. Visual acuity was reduced to 20/400 in the right eye and 20/155 in the left eye.

Both patients responded well to hormone therapy, with rapid improvement in the first three days and continued improvement during the period of treatment. As the vitreous cleared, in case 23, an intense, generalized edema of the retina was revealed near the posterior pole of each eye; this gradually diminished with treatment.

In case 22, occasional cells in the anterior chamber and a few keratic precipitates on the endothelium appeared approximately one week after termination of parenteral therapy. These gradually disappeared with the topical use of cortisone. The patient has been free of activity for the past two months, while in case 23 there has been no evidence of recurrence in a three week follow-up period. In neither case could any residual pathologic sign be seen in the fundus after termination of therapy.

*Acute Optic Neuritis.*—Three patients with optic neuritis were treated with hormone therapy—one with ACTH and two with cortisone.

CASE 24.—Three months prior to admission the patient lost all vision except for vague light perception in one eye, owing to an inflammation similar to that for which he was hospitalized. This occurred despite intensive therapy with vasodilators, antibiotics, thiamine chloride and foreign protein. Three weeks before his admission to the hospital vision in the remaining eye became blurred and within 24 days decreased to light perception only. During this interval he received no treatment. Just prior to hormone therapy vision decreased to the point where it was impossible to plot the field on the tangent screen with use of a muscle light. Figure 3 shows the response to therapy. At the time of this report, after three months, the visual field remains the same, but visual acuity has regressed to 20/100. The eye with the older disease process showed no improvement with the ACTH therapy.

CASE 25.—The second patient, a young woman, had a more typical retrobulbar optic neuritis. She gave a history of sudden blurring of vision in one eye four weeks prior to treatment. At the time of admission visual acuity was reduced to 20/155, with very slight blurring of the nasal margin of the disk and four petechial hemorrhages in this area. No target smaller than 3 mm. white was seen on the tangent screen at 1 M., and this area of vision was limited to 20 to 25 degrees. Blue was not seen and red was seen vaguely with a 5 mm. target at 1 M. in a central area of 5 to 15 degrees. Two hours after the first 50 mg. dose of cortisone, the 1 mm. target was seen at 1 M. over a central area of 10 to 15 degrees. The field for 5/1000 was enlarged, and for the first time there was a field for 5/1000 blue of 4 to 10 degrees. Visual acuity had improved to 20/60. Within 24 hours the fields for red and blue had attained almost normal proportions, but the field for 1/1000 white remained essentially unchanged, as did the visual acuity. At the conclusion of treatment visual acuity was 20/20, and the visual fields were well within normal limits.

CASE 26.—There was blurring of the disk margin with a small amount of exudate and an area of retinal edema extending from the disk temporally and below the macula. Visual acuity was 20/109. Tangent screen examination revealed a greatly enlarged blindspot and

an absolute scotoma corresponding to the area of edema. At the end of the seventh day of therapy the tangent screen examination revealed a normal field, and visual acuity had improved to 20/25. Six weeks after the patient's discharge from the hospital the visual field remained normal and visual acuity was 20/20.

*Chronic Iridocyclitis.*—Five patients with chronic iridocyclitis were treated with ACTH. Four of these had bilateral and one had unilateral inflammation. The inflammatory reaction had been present continuously for periods varying from seven months to four years. Four of the five patients had been subjected to extensive treatment, including repeated courses of foreign protein therapy, administration of old tuberculin and antibiotics and continued use of atropine. All patients had been thoroughly studied on repeated occasions in an effort to deter-

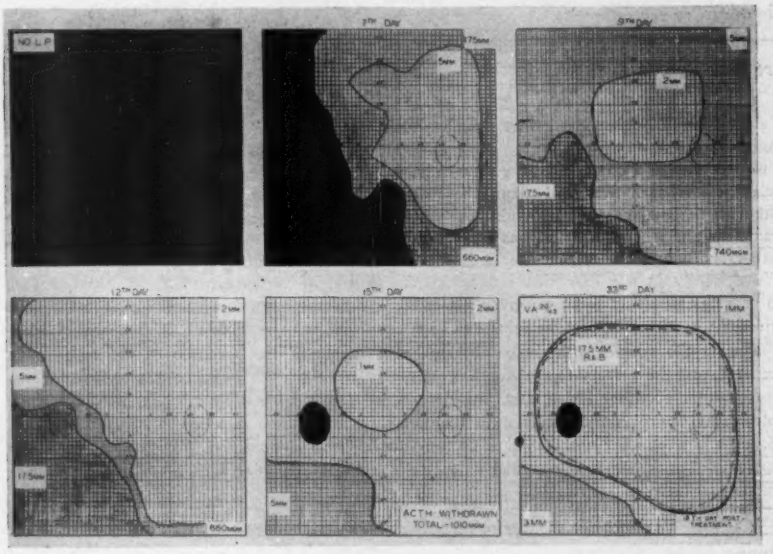


Fig. 3 (case 24).—A series of tangent screen studies taken at 1 M., showing progressive improvement in fields and visual acuity in a patient aged 47 with optic neuritis (left eye) of three weeks' duration. Treatment was with 1,010 mg. of ACTH over a 15 day period. A dose of 20 mg. was given every four hours from the first to the third day, every six hours from the fourth to the sixth day and every eight hours from the seventh to the thirteenth day, inclusive; and 10 mg. was given every six hours on the fourteenth and fifteenth days.

mine an etiological agent. Patient 30 had bilateral involvement and far advanced crippling rheumatoid arthritis, while another (patient 29) had sarcoidosis, as proved by biopsy. The latter had three small nodules on the iris of one eye. The cause of the lesions could not be proved in the other three cases, although in a case of bilateral involvement the Wassermann reaction was 4+ and roentgenograms showed changes suggestive of sarcoidosis. One of the five patients gave a positive reaction to 0.1 mg. of old tuberculin.

At the time these patients were first seen for consideration of hormone therapy only two had ocular pain. This was due to a superimposed, acute exacerbation

with fibrinous exudate in case 27 and to secondary glaucoma resulting from iris bombé in case 28. The glaucoma was controlled by transfixation of the iris. Physical findings in the five cases were characteristic of the process and varied slightly according to the severity and duration of the condition.

The response of these patients to treatment was gradual but definite. This was evidenced by the gradual reduction in cells and keratic precipitates. In two cases the resolution was complete at the conclusion of treatment, while minimal signs remained in the other three cases. In each instance a recurrence to approximately the pretreatment level occurred within a period of one to 10 weeks.

It is of interest to note that the nodules in the iris in case 29 had disappeared in 10 days and have not recurred. In the same case, however, repeated roentgenograms of the chest during and after the course of therapy have revealed no change.

*Central Chorioretinitis.*—Two almost identical cases of central chorioretinitis are reported.

CASES 31 and 33.—In each case the opposite eye had previously lost central vision through a similar process, but these lesions were quiescent and well pigmented. In both cases the fresh lesion was paramacular, sharply circumscribed to about 1 disk diameter in size, elevated 4 to 6 D. and of a characteristic yellow-gray, mottled appearance. Both showed minute superficial hemorrhages over and about the margins of the lesions. Exudate was not present, although minimal edema surrounded the lesion and invaded the macular area. The vitreous was clear and free of cells, as was the anterior chamber. The onset in each case had occurred rather suddenly three to four weeks previously, with blurring of vision as the only symptom. Visual acuity in one case was reduced to 20/60, and in the other, to 20/68. In one case no previous treatment had been given, while in the other artificial fever, antibiotics, intravenous injections of histamine and vitamins had been employed, with little or no change in the lesion.

During the course of hormone therapy, a reduction in the elevation of the lesions had occurred, and the surrounding edema had subsided. No appreciable change was observed in the size or color of either lesion, and, although visual acuity in each case improved to 20/32, no noteworthy improvement occurred in the tangent screen findings after the edema subsided. Within one week after withdrawal of therapy lesions were again active in each case, with fresh superficial hemorrhages, edema and extension toward the macular area. Vision was proportionately reduced in both cases.

*Chronic Exudative Posterior Uveitis.*—Only one patient was studied in this group.

CASE 34.—The left eye had been enucleated five years previously because of chronic inflammation. Nine months prior to the patient's admission for ACTH therapy, he had a sudden onset of blurred vision, which increased in spite of foreign protein and antibiotic therapy. On his admission, the only finding was dense clouding of the vitreous, with no localizing choroidal lesions. Visual acuity was reduced to 20/52 with correction, and the central visual field was reduced to 5 to 10 degrees.

With therapy there was a gradual increase in the size of the central field to 15 to 18 degrees, but there was no appreciable change in the visual acuity or in the appearance of the vitreous. Two weeks after withdrawal the visual field was again reduced to nearly pretreatment level. There has been no change in the succeeding three months.

### DEGENERATIVE DISEASE

In contrast to the definite response to hormone therapy shown by acute and chronic inflammatory disease, the diseases usually classed as degenerative failed to show any appreciable response to treatment. Changes in the fundus were well

established in each of the cases studied, and it was not anticipated that the process would reverse.

Degenerative ocular lesions were treated with ACTH in four cases.

In case 35, one of Kuhnt-Junius disciform degeneration of the macula, no improvement in visual fields or in visual acuity followed treatment. Repeated observations in the succeeding three months showed continued progress of the lesion.

In case 36, there were extensive angioid streaks of the retina with involvement of both maculas. Pseudoxanthoma elastica was present on the neck, in the axillary folds and in the groin. There was no response to therapy.

In case 37, the development of bilateral pigmentary degeneration of the macula had been watched over a period of four months preceding treatment. Although the duration of treatment was perhaps short, the dose was adequate as measured by the laboratory indexes. Not only was there no apparent improvement under treatment, but during a four month follow-up period the pigmentary degeneration has progressed.

In case 38 there were bilateral pigmented retinitis and absolute glaucoma in one eye. In the other eye intraocular tension was 27 mm. (Schiøtz) and visual acuity was reduced to 8/200. The patient was able to see only a 17.5 mm. white target at 1 M. in a limited central area. No improvement in visual acuity, visual fields or intraocular pressure occurred during therapy.

### HEREDITARY DISEASE

*Retinitis Pigmentosa.*—Two patients with retinitis pigmentosa were treated, one with ACTH and one with cortisone.

Case 39.—The first patient did not receive placebo treatment, and biophotometric readings were not made. It is doubtful whether any dark adaptability could have been recorded in this case because of the extensive pigmentation, which included all areas of the retina to the macula. There were numerous areas suggestive of old chorioretinitis and atrophy of both optic disks. Visual acuity was reduced to 20/200 — 1 in each eye, and he was unable to read better than Jaeger type 10 with either eye. Visual fields for targets of all sizes were reduced to within 5 degrees. Colors were not distinguished.

The left eye, which was the more severely damaged, showed no appreciable improvement under therapy, but four hours after the first 20 mg. dose of ACTH visual acuity in the right eye improved to 20/97. There was no improvement in the visual field. On the third day the visual acuity had improved to 20/68, and the patient was able to read Jaeger type 4. He stated that for the first time in four years he was able to read newsprint. Over the succeeding three days no additional improvement was noted; so treatment was withdrawn. Visual acuity has remained 20/68 during the four month follow-up period, without change in the visual fields or the fundi.

Case 40.—A 9 year old boy, from a family with retinitis pigmentosa, showed only mild pallor of the disks and a few flecks of pigment in the extreme periphery of the fundus. The vessels were slightly attenuated. Visual acuity was 20/38 in each eye, and the three tangent screen examinations prior to therapy showed a reduction for 2/1000 and 5/1000 white to from 10 to 15 degrees from the fixation point. Fields for 5/1000 red and blue were reduced to approximately 5 degrees from the fixation point, blue being identified as green. Three pre-treatment biophotometric examinations were made to establish a base line, and these all gave consistent results. In view of his age, the patient was not subjected to placebo treatment. Administration of 25 mg. of cortisone every six hours resulted in definite improvement in both the biophotometric readings and the visual fields in the first 24 hours. The improvement continued through the second day of treatment, leveling off until the dose of the drug was increased on the seventh day to 50 mg. every six hours. There was then gradual improvement in the biophotometric readings until the eleventh day. This level was maintained through the fourteenth day, after which cortisone therapy was discontinued. No changes in the fundus could be noted, and visual acuity did not improve beyond 20/38. Visual fields have been maintained in the 10 weeks since withdrawal, but the biophotometric readings have tended to show regression.

MISCELLANEOUS DISEASES

*Herpes Zoster Ophthalmicus.*—CASE 41.—A vesicular eruption corresponded to the distribution of the ophthalmic branch of the fifth cranial nerve (fig. 4), without involvement of the nasociliary nerve. There were edema of the right upper lid, moderate conjunctival injection and a 2 + cell count in the anterior chamber, with numerous small punctate areas in the cornea, which stained with fluorescein.

Pain over the involved cutaneous areas disappeared four hours after the initial injection of ACTH. The vesicular lesions became encrusted at the end of 24 hours. The only finding at the end of the third day was an occasional cell in the anterior chamber and a small amount of cellular debris on the endothelium, with total disappearance of cells by the sixth day. One week after cessation of therapy there were a few cells in the anterior chamber, an occasional small keratic precipitate and slight recurrence of circumcorneal injection. During a subsequent nine days of topical treatment with cortisone these lesions entirely disappeared, and three weeks after withdrawal of the topical therapy there was no evidence of any inflammatory reaction and the patient was asymptomatic.

Fig. 4 (case 41).—Herpes zoster ophthalmicus with corneal changes and iridocyclitis. Pain disappeared four hours after initial dose of 20 mg. of ACTH. Appearance (*A*) before treatment, (*B*) after 24 hours of therapy, (*C*) after three days of treatment and (*D*) after seven days of treatment. There were no ocular manifestations after the third day of therapy. The cell count in the anterior chamber was 2+ one week after therapy, and this level was controlled by topical cortisone therapy.

*Acne Rosacea Keratoconjunctivitis.*—CASE 42.—The patient had a long history of acne rosacea. Three years previously he had lost his left eye as a result of severe rosacea keratoconjunctivitis.

One year prior to his admission, keratoconjunctivitis developed in the right eye. This gradually progressed, despite intensive therapy with foreign proteins, antibiotics and radium D (radioactive isotope of lead). At the time of his admission for ACTH therapy there was a dense central corneal conglomerate, 3 mm. in diameter, nourished by a very large stromal vessel which showed arborization at the central point. There were conjunctival injection, moderate corneal bedewing and intense pain and photophobia. The findings in general were comparable to those in his left eye in the month preceding enucleation.

There was a dramatic response to treatment. In less than four hours after the first 20 mg. dose of ACTH all pain and photophobia had disappeared, and for the first time in eight

months the patient was asymptomatic. Within 24 hours, corneal edema disappeared, the area of central corneal infiltration was reduced in size and density and there was less engorgement of the corneal vessels. The central corneal infiltration was reduced to one-half its original size by the third day. At this time the conjunctiva was entirely clear, and the corneal vessels showed considerable reduction in size. Furthermore, the lesions of acne rosacea on the skin were clearing. There was continued improvement during the course of therapy until the dose was reduced to 60 mg. per day. At that time there was some recurrence of corneal edema and circumcorneal injection. The eosinophil count had returned to the pretreatment level, and it was obvious the patient was getting no effect from the drug in that dosage.

He was then placed under topical treatment with cortisone. Twenty-four hours later the corneal edema had disappeared and the conjunctival reaction was minimal. Under continuing treatment with topical applications of cortisone, the eye remains clinically free from active disease.

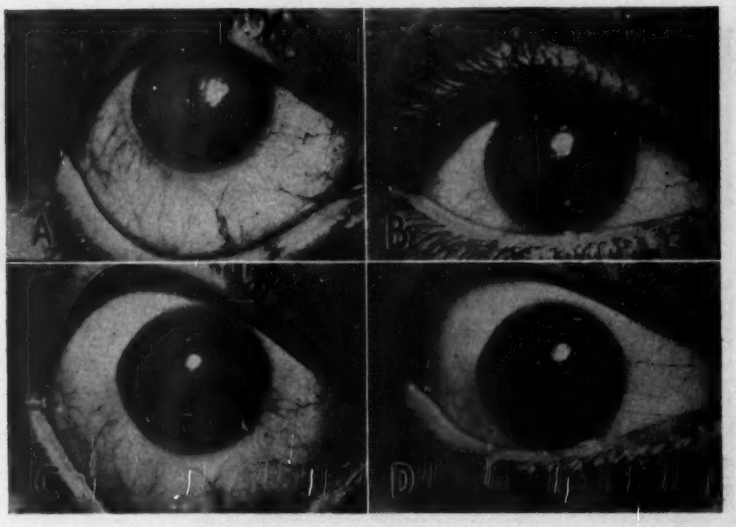

Fig. 5 (case 46).—Atypical congenital syphilitic keratitis in a 15 year old girl. The series shows improvement after treatment with ACTH (three days), parenteral administration of cortisone (11 days) and topical instillation of cortisone (six weeks). Appearance (*A*) before treatment, (*B*) after seven days of treatment, (*C*) after 25 days (11 days of topical cortisone therapy) and (*D*) after two months (end of treatment).

*Vitreous Abscess.*—Case 43.—A woman with severe diabetes was admitted for therapy after the development of a vitreous abscess in the fifth week following intracapsular cataract extraction. She had received intensive prolonged antibiotic and foreign protein therapy, as well as topical instillation of sodium sulfacetimide and subconjunctival injections of penicillin and streptomycin. Despite this regimen the condition progressed to full abscess formation. The parenteral administration of antibiotics was continued after her transfer to this hospital for ACTH therapy. Four hours after the initial dose of 20 mg. of ACTH pain disappeared. Seventy-two hours later chemosis and edema of the lids had subsided, and the inflammatory process appeared to be arrested. The anterior chamber was free from circulating cells. When ACTH was discontinued, she remained free from symptoms and without evidence of recurrence as long as the antibiotic therapy was maintained. A severe hemorrhage into the anterior chamber occurred on withdrawal of the antibiotics, and the inflammatory reaction again became apparent. Further medical therapy did not appear advisable.

*Anterior Granulomatous Scleritis.*—Case 44.—This case was previously reported [1] as one of severe keratitis and anterior uveitis. Continued study, however, has suggested the diagnosis of anterior granulomatous scleritis. As reported, there was a good response to ACTH with almost complete remission. One week after termination of ACTH therapy there began a gradual regression to the pretreatment level and topical applications of cortisone were started. With this treatment the inflammatory reaction has been controlled for three months.

*Severe Postoperative Keratitis with Iridocyclitis.*—Case 45.—In this case, which was previously reported,[1] the response to ACTH was incomplete and a relapse to the pretreatment level occurred one week after cessation of therapy. There was a gradual deterioration in the patient's condition during the next two months, and she was then placed under topical cortisone therapy. The conjunctival injection and corneal bedewing had almost cleared in 10 days, and the improvement has been maintained under continuous topical cortisone therapy.

*Atypical Congenital Syphilitic Keratitis.*—Case 46.—In this case, also previously reported,[10] the patient had received ACTH and parenteral and topical cortisone therapy. The topical use

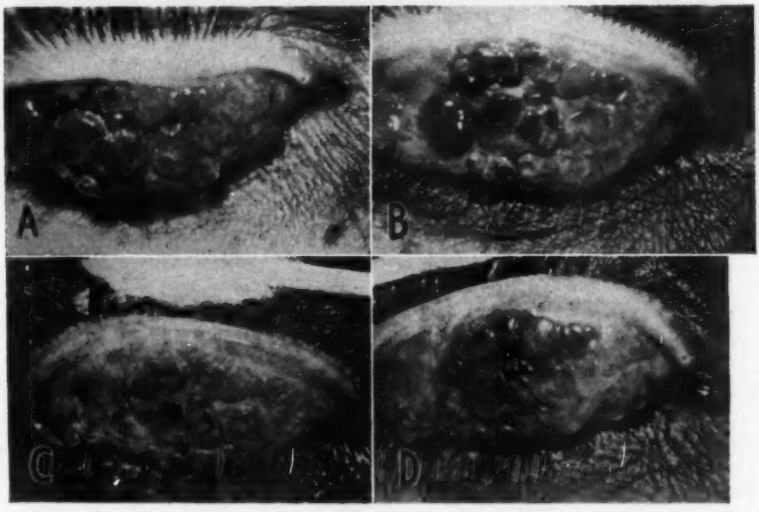


Fig. 6 (case 47).—Severe vernal conjunctivitis of 12 years' duration. The series shows response to ACTH during two weeks of therapy. Symptoms and signs recurred two weeks after therapy was discontinued, with no sustained response to topical use of cortisone. (*A*) before treatment, (*B*) after five days of therapy, (*C*) at end of treatment (14 days) and (*D*) 17 days after termination of treatment.

of the drug was continued after her discharge from the hospital. Six weeks later only a faint central opacity (fig. 5) was observed, when previously there had been extensive bilateral corneal involvement. Amenorrhea of two months' duration resulted from the parenteral therapy.

*Vernal Conjunctivitis.*—Case 47.—The vernal conjunctivitis in this case, present for 12 years, had not responded to any type of extensive therapy, including surgical and roentgenologic measures. The severity of this condition and its subsequent changes during and after treatment are shown in figure 6. Biopsy before treatment revealed the usual intensive eosinophilic infiltration, edematous stroma and many chronic inflammatory cells. On the eighth day of treatment a second biopsy revealed complete absence of inflammatory reaction and eosinophilic infiltration. Symptomatic relief was complete in three days, but there was a recurrence of severe itching and mucoid discharge after withdrawal of ACTH. For two weeks there was little change in the conjunctiva, but in the succeeding month the "cobblestone" papillae increased

in size. At the time of this report, they have not approached their original proportions. Topical use of cortisone was ineffectual.

*Transitional Cell Carcinoma of Limbus.*—CASE 48.—The patient was admitted with the diagnosis of early phlyctenular keratoconjunctivitis. In figure 7 is shown the reduction in vascularity which followed four days of ACTH therapy. The lesion relapsed to the pretreatment level 12 days after use of the drug was discontinued. During the following month it continued to enlarge, becoming more neoplastic in appearance. Excision at the end of this period revealed a transitional cell carcinoma of the limbus, grade I.

*Optic Nerve Atrophy.*—CASE 49.—Optic atrophy had developed two years prior to the present admission, after an attack of acute retrobulbar neuritis. There was no response to 21 days of intensive ACTH therapy.

*Glaucoma.*—CASE 50.—A patient with untreated bilateral chronic simple glaucoma had an intraocular tension of 55 mm. of mercury (Schiøtz) in the right eye and of 48 mm. in the left eye. With ACTH therapy the pressure decreased temporarily to 30 mm. in the right eye and 27 mm. in the left eye and returned to the original level in 24 hours, at which time therapy was discontinued. There was an immediate response to miotics.

CASE 51.—Acute congestive glaucoma developed in an aphakic eye five weeks after cyclodialysis for chronic secondary glaucoma. Administration of 300 mg. of cortisone in 36 hours failed to alter the intraocular pressure.

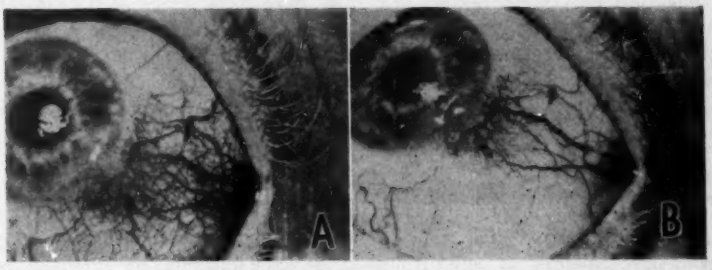


Fig. 7 (case 48).—Transitional cell carcinoma at the limbus. The original diagnosis was phlyctenular keratoconjunctivitis, and the condition was treated with ACTH. Note the marked diminution of inflammation surrounding the lesion, suggesting unwarranted optimism for the therapy. (*A*) before treatment, (*B*) 24 hours after beginning of treatment.

It should be noted here, however, that the glaucoma secondary to inflammatory processes in four patients of the acute group responded with the same rapidity as did the reduction in inflammation.

## PHYSIOLOGICAL SIDE EFFECTS

This aspect of ACTH and cortisone therapy will be considered briefly. In table 1 are presented the observations on changes in body weight and blood pressure, in addition to the laboratory data. In tables 1 and 2 the observed side effects are recorded.

It will be noted that minimal increases in blood pressure were seen in a number of patients receiving either ACTH or cortisone. In five patients the increase in the systolic level was 25 mm. of mercury or more, and in six the diastolic increase was 20 mm. or more. Three patients (cases 9, 10 and 25), none of whom were hypertensive, had a significant lowering of blood pressure with cortisone therapy, while two patients (cases 31 and 36) had reductions with ACTH therapy. Return to control levels was noted in all patients at the conclusion of treatment.

Moderate increases in body weight were seen in most patients receiving ACTH, while in seven of the 14 patients receiving cortisone either no change or a reduction in weight was observed during therapy. Clinically demonstrable edema was present in only two patients receiving ACTH (cases 15 and 47), but minimal soft tissue swelling was not uncommon. This was not observed in patients treated with cortisone.

Mild to moderate transient acne appeared in five patients (cases 16, 17, 38, 42 and 47) receiving ACTH. Amenorrhea, of two months' duration, was observed in a young girl (case 46) receiving first ACTH and then cortisone for a total of 240 and 2,450 mg., respectively.

Significant changes in the mental status of patients in this series were not encountered. In many exhilaration and a sense of well-being were experienced. Even more commonly encountered was the transient period of "let-down," sometimes mild depression, which followed the withdrawal of ACTH.

The following changes, though not considered physiological, were noted as side effects. In case 45 auricular fibrillation appeared during the administration of ACTH, but this could not be attributed to the effects of the hormone. Repeated spontaneous epistaxes developed in case 47 during the period of ACTH therapy. Studies revealed normal thrombocyte counts and abnormal prothrombin and clotting times. No further bleeding has followed the withdrawal of ACTH. In three patients an inexplicable variable increase in temperature of from 0.5 to 1.5 degrees (F.) was observed during the period of administration of cortisone, falling to normal or below on withdrawal of the drug.

## COMMENT

Without question, both ACTH and cortisone have a definite role in the treatment of ocular disease. The results to date have shown clearly that these hormonal agents have produced far better results in the acute inflammatory lesions of the eye than in any other category of ocular disease. Of 26 patients with acute inflammatory disease of the eyes treated with ACTH and cortisone, successful results were obtained in all but one. It should be pointed out that only the control of the acute active phase is now under discussion, and not the usual course of inflammatory ocular disease, which is frequently recurrent. It should be emphasized that the tendency toward recurrence is not influenced by hormone therapy.

The explanation of the one failure in the group with acute inflammatory disease is not entirely apparent. The patient (case 7) had active iridocyclitis for two months, which had been treated on an ambulatory basis without achieving complete control. By the time she was admitted for hormonal treatment certain features of chronicity may have developed, and it is possible that this patient might better have been classified with the chronic group.

It is not surprising that the results in the group with chronic inflammatory disease did not approach those obtained in the acute group. This is in agreement with the recent report of Gordon and McLean.[13] Chronic disease in general implies that the patient has achieved at least a near equilibrium with the inciting factor and that more permanent types of pathological changes have been established. The improvement observed in eight of the nine patients with chronic inflammatory

13. Gordon, D. M., and McLean, J. M.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy in Ophthalmologic Conditions, J.A.M.A. **142**:1271-1276 (April 22) 1950.

disease was, for the most part, a reflection of reversal of the concurrent active manifestations. By this we mean the clearing of free cells, keratic precipitates and circumcorneal injection. It is of real interest that within one to 10 weeks of cessation of hormonal therapy these features returned in every case. Of equal importance is the fact that in neither the acute nor the chronic inflammatory groups did the more permanent changes, such as atrophy of the iris, synechias or lenticular opacity, undergo any visible alteration. It would seem that neither ACTH nor cortisone offers any real promise for the cure of chronic ocular disease. In a sense, this can be qualified by stating that repeated or prolonged administration of these agents in smaller doses may prevent the progression of the "active" features that commonly accompany chronic disease. This aspect of therapy has not been covered in the present study and will require long term observations by many investigators. This applies not only to ocular disease but to all types of chronic inflammation.

*Degenerative Diseases.*—In the group of degenerative diseases, as would be expected, there was no improvement in either the subjective or the objective features of disease. Two of the four patients (cases 35 and 37) received minimal treatment—260 mg. over a four day period and 140 mg. over a seven day period, respectively. It is difficult to conceive on pathophysiological grounds of any benefit that would have resulted, but longer periods of study may be indicated in some cases.

*Hereditary Diseases.*—Although these diseases are unquestionably transmitted by genetic factors, they are in a sense degenerative, and their separation from the foregoing group is only arbitrary. Results of investigations of these conditions are difficult to evaluate. With rigid controls, a number of patients with retinitis pigmentosa are presently undergoing hormonal therapy, but treatment and follow-up studies are incomplete. Exposure to any new therapy tends to bring about subjective improvement, since patients with retinitis pigmentosa are prone to suggestion. In unpublished studies by one of us (E. H. S.) a decided subjective improvement was noted, without change in visual acuity, visual fields or biophotometric readings during a period of saline placebo therapy.

Two patients with retinitis pigmentosa, one a child of 9 years with early manifestations of disease and the other a man with far advanced lesions, have received cortisone and ACTH, respectively. In the case of the adult, improvement in visual acuity was recorded over the first three days of therapy. In the light of the foregoing remarks, it is impossible to determine how much improvement was psychological or how much was induced with hormones.

In the boy with early disease, psychological factors were not considered of any real influence on the response. Here, unquestioned benefit was seen within the first 24 hours of parenteral administration of cortisone, and gains continued through the eleventh day. Improvement was limited to changes in the visual fields and in dark adaptation. It is of interest to note that when improvement did not continue with a dose of 100 mg. per day further gains were observed when the dose was increased to 200 mg. on the seventh day. Again, improvement ceased after four days of therapy. The visual fields have been maintained, but biophotometric readings have regressed in the five week period of follow-up study. Obviously, much remains to be investigated in the hormonal treatment of hereditary ocular diseases.

*Miscellaneous Diseases.*—The group of miscellaneous diseases cannot be discussed categorically, nor does it appear proper to draw broad conclusions from the limited experience in treating one or another of this group.

The results of ACTH therapy in the patient with herpes zoster ophthalmicus were very gratifying but cannot be said to have been superior to those in patients successfully treated with immune transfusions. This is true with respect both to the control of symptoms and to the rate and completeness of regression in the lesions themselves. It is of note that the mild iridocyclitis, which was present when ACTH was withdrawn, responded completely to topical use of cortisone.

The patient with severe acne rosacea keratoconjunctivitis had a gratifying response to ACTH. This is notable in view of the refractoriness which has characterized previous treatment of patients with such advanced lesions. As in previous cases, topical applications of cortisone have controlled effectively the minimal inflammatory process which in this instance was considered a partial relapse. It is too early to classify this response as a complete cure.

The result of ACTH therapy in the diabetic patient with an abscess of the vitreous is of interest primarily in the fact that when this hormone was administered in conjunction with antimicrobial agents the acute process was arrested. The ACTH appeared effectively to enhance the action of the antimicrobial drugs. This is suggested by the fact that prior to hormonal administration these agents did not control the lesion and that during administration and on withdrawal of the ACTH they were able effectively to limit the activity. In turn, when these were withdrawn, a complete relapse followed.

The case of anterior granulomatous scleritis (case 44) and that of postoperative keratitis with iridocyclitis (case 45) have been reported previously.[1] The results during ACTH therapy were no more than partial remissions, and complete relapse occurred on withdrawal of the drug. Both patients have attained levels of response to topical use of cortisone that were observed with parenteral therapy. Again, one cannot classify these results as "cures," and the final outcome awaits further observation and study.

We are reluctant to draw any conclusions as to the therapeutic benefit that might have accrued from any one of the forms of hormonal therapy employed in the patient with atypical congenital syphilitic keratitis. It appears, however, that the total treatment with ACTH and the parenteral and topical administration of cortisone, in turn, materially benefited the patient and that a satisfactory result was obtained.

Vernal conjunctivitis has been notoriously resistant to therapy in the past. In case 47 a striking reduction in the severe lesions occurred with ACTH therapy. The severity of this lesion, its refractoriness to previous therapy and its striking, but temporary, response to ACTH suggest that interrupted therapy with the latter may be a means of achieving some degree of regression.

The only discussion which seems indicated in the case of transitional cell carcinoma of the limbus (case 48) is to point out that the associated inflammatory processes were controlled during the period of administration of ACTH. The correct diagnosis was not established until after treatment was discontinued. The lesson to be learned in this case is that even inflammatory response to malignant change may undergo some resolution with these hormonal agents and that an

incorrect diagnosis may lead to an unfavorable course if such changes are used as diagnostic indexes.

The use of either cortisone or ACTH in the treatment of optic nerve atrophy would not be expected to produce benefit. This attitude prevailed prior to the administration of ACTH to the one patient (case 49) with this disease and the complete therapeutic failure was in no way surprising.

The limited number of patients with primary glaucoma does not allow any categorical statement as to the benefit from these hormonal agents. The two patients, one with chronic simple glaucoma (case 50) and the other with acute congestive glaucoma (case 51), received no sustained benefit from short periods of treatment. It is possible in the future that some patients with early primary glaucoma might benefit temporarily from ACTH and cortisone through the often encountered effect of these hormones on the mental state of the patient. In this sense, the benefit may not be materially different from that achieved by sedation therapy. Careful evaluation of their place in the treatment of primary glaucoma is obviously necessary. It would appear to be limited.

*Comparative Aspects of ACTH and Cortisone.*—In this study there has been no significant difference in the therapeutic results obtained with ACTH and those with cortisone. Both have proved highly effective in the resolution of the acute inflammatory lesions. It is too early to make a comparison of the early relapse rates in acute iridocyclitis, the only group in which comparable numbers have been studied, but the recurrence of activity in three of six cases in which cortisone was used is in contrast to the early recurrence in only one of the six cases in which complete remission was obtained with ACTH. This suggests that cortisone may have a final higher relapse rate than ACTH. All these relapses occurred within a two month period, and seemingly it is not justified to compare the respective long term relapse rates, for two reasons. First, the duration of follow-up study in many cases has not been long enough and, second, the longer term relapse rate is, unquestionably, a reflection of the basic nature of the disease rather than of the method of therapy during the acute phase. We do not feel that either ACTH or cortisone will have any influence on the long term relapse rate in cases of acute recurrent inflammatory disease.

There is a physiological consideration which would lead one to believe that the early relapse rate for cortisone might be higher than that for ACTH. The physiological restoration of normal anterior pituitary-adrenal cortex activity after exogenous ACTH therapy is accomplished within a few days. Cortisone, by its direct inhibition of cortical function, and by depressing the activity of the anterior lobe of the pituitary, may require longer periods before intrinsic mechanisms are restored.

No statement is permissible as to the comparative merits of these two agents in the treatment of chronic inflammatory lesions. The series does not include any of this type that has received cortisone, since ACTH, initially, was employed more widely to determine the possible therapeutic value of these two agents in the general field of ocular disease.

One must give serious consideration to the idea that ACTH, and possibly cortisone, may achieve superior results through interrupted courses of therapy or in smaller doses over longer periods. This possibility is currently under investigation. Although it is too early to state, physiological considerations suggest that

ACTH may have greater desirability through its lack of inducing adrenal involution during long term therapy.

The patients treated with these hormones in the other categories of ocular disease are too few to justify further discussion.

*General Considerations.*—These agents must be evaluated in the light of the current foreign protein therapy. With both ACTH and cortisone the over-all results obtained are equal, if not superior, to those achieved by present day methods of therapy. It is unquestioned that both subjective and objective improvement have been accomplished in significantly shorter periods. Although greater rapidity of action is often a desirable feature of a therapeutic agent, the final result is the critical basis for comparison. In this respect, again, both ACTH and cortisone therapy of the acute inflammatory lesions has certainly been equal, if not superior, to standard methods now employed. Moreover, in this series there were 16 patients with lesions proved refractory to the usual therapeutic measures who received unquestioned benefit from the hormonal treatment. It is perhaps in this group of patients that both ACTH and cortisone will achieve their greatest distinction.

The use of ACTH and cortisone in the treatment of ocular inflammatory disease has not yet shed any real light on the pathogenesis of these lesions. From the excellent results we have achieved in the treatment of the acute inflammatory lesions, and from our evaluation of the circumstances in which these lesions appeared in many patients, we may entertain several hypotheses. The presence of focal infection has been widely acknowledged as a possible etiological factor in the inception of inflammatory disease through a hypersensitivity response in ocular tissue. If so, then ACTH would be effective in temporarily blocking this change, as it has in a variety of hypersensitivity states. In this respect, the continued search for and eradication of focal infection are indicated, and the use of neither ACTH nor cortisone should eliminate this. The later relapse of acute disease may hinge on their continued presence.

In another sense, the eye, by virtue of changes in its vascular bed, fluid media and tissues of mesenchymal origin, may reflect alterations in the pattern of adrenal cortex activity. If so, some inflammatory diseases may have origin in persons in whom abnormal adrenal activity has developed. In these, hypersensitivity may be of little consequence, and the disease may be directly related to disturbed patterns of adrenal steriod secretion. In some patients the breakdown of tissue may occur during prolonged stress, and into this category appear to fall many of the patients with acute inflammatory lesions who were followed in this series. As such, these ocular lesions would fall into the general classification of diseases of adaptation as conceived by Selye.[8] That ACTH should be effective in treatment of these patients is not readily apparent, but it is possible that relative steroidal deficiencies are corrected. This is more plausible when one considers that the total response to stress, with its involvement of epinephrine and the entire sympathetic nervous system, is quite different physiologically from the relatively simplified response to exogenous ACTH.

As a final and practical consideration, it should be emphasized that, although ACTH and cortisone have here been used without encountering any deleterious effects, the application to ophthalmology, as in all fields, must be guided by sound physiological thought, with constant attention to the several undesirable features that may arise from their misuse.

SUMMARY

The results of the experimental use of adrenocorticotropic hormone (ACTH) and cortisone in the treatment of 51 patients with a wide variety of ocular lesions are reported. Of these, 37 patients have received ACTH, and 14, cortisone.

Excellent results were obtained in the group with acute inflammatory lesions, with rapid and complete resolution in most cases. Here, both ACTH and cortisone gave comparable results and appear superior to the currently employed methods of therapy. In certain cases of inflammation of the anterior segment of the eye relapses were successfully treated with topical instillations of cortisone.

Chronic inflammatory diseases showed a definite, but transitory, response under the currently used brief intensive method of therapy. In this group the value both of interrupted and of sustained, less intensive therapy is currently under investigation.

No response in treatment of degenerative disease, primary glaucoma and optic nerve atrophy was observed. In retinitis pigmentosa a limited response occurred, but this cannot be properly evaluated until treatment is completed in a larger group now under study. In one case of vernal conjunctivitis a striking but temporary improvement was observed.

Methods of treatment are discussed, and the results of laboratory studies as a guide to therapy and for the protection of the patient are presented. In some patients minor physiological side effects were observed, but in no instance did this significantly alter the course of therapy. No true complications were observed.

The rationale for the use of ACTH and cortisone in ocular inflammatory disease is discussed on physiological grounds and on the basis of the present understanding of the etiology of these ocular diseases.

## ABSTRACT OF DISCUSSION

DR. KENNETH C. SWAN, Portland, Ore.: We are indebted to Dr. Olson and his co-workers for this review of the largest series of patients with ocular diseases yet to be treated with ACTH and cortisone. The authors observed that the most consistent responses occur in acute inflammatory processes. The exact mechanism of action of ACTH and cortisone in these processes has not been established with certainty; however, there is no evidence that cortisone acts directly on any exogenous injurious agent, such as bacteria, or influences inflammatory disease by correction of a deficiency or hormonal imbalance; therefore, it cannot be said that either ACTH or cortisone cures any ocular inflammation in the sense of removing the cause of the disease. As stressed by the authors, these hormones are not substitutes for the antibiotics or other agents. The major effect of cortisone in treatment of inflammatory disease seems to be blockage or alteration of responses of certain tissues to injury. This is not the sole action, but this concept provides a working basis for the prescription of these drugs for ocular inflammations.

There are a number of conditions in which the major damage to vision and to the globe comes from excessive tissue response rather than from direct injury. For example, in anterior uveitis, vision is impaired or threatened less by focal injury to the iris or ciliary body than by the exudative tissue reaction, which leads to occlusion of the pupil, formation of synechias, secondary glaucoma, etc. It appears that ACTH and cortisone, by controlling these excessive and injurious reactions, will provide, for the first time, a means of preventing many of the complications and sequelae of inflammatory disease which destroy vision.

Clinical trials with ACTH and cortisone have far outdistanced the experimental studies, largely because these drugs have offered the only hope for certain desperate

conditions. Much remains to be determined about the dosage and side effects, and the possibility of delayed or indirect detrimental effects has scarcely been investigated. It would seem wise if, for the present, use of these compounds were restricted to serious cases in which something would appear to be gained by the inhibition of excessive inflammatory reaction. There is no longer an excuse for the haphazard administration of these drugs for every recalcitrant ocular problem or as a substitute for accurate diagnosis and specific etiological therapy.

DR. THOMAS CAVANAUGH, Boston: The authors of this paper are to be commended on their presentation of such a clear and well documented report on the use of ACTH and cortisone in the treatment of ocular diseases. It is not in my province to add to this paper except indirectly. The secretary of our Section requested me to offer you a new approach to the treatment of certain ocular diseases and to point out how massive doses of ascorbic acid produce a clinical response similar to that of ACTH and cortisone, suggesting that in the future it will be necessary to try to evaluate the relation of ACTH and cortisone to ascorbic acid. Therapy with massive doses of ascorbic acid was originally introduced at the Newton-Wellesley Hospital by Dr. Frank O'Connor in 1949 in the treatment of various types of arthritis. Since arthritis and uveitis are not uncommonly associated, it was felt that ascorbic acid might be of value in the treatment of cases of the latter, and later ascorbic acid was employed in various other types of disease of the anterior and posterior segments.

It is well known that the role of cholesterol and ascorbic acid in the in vivo production of adrenocortical hormones has been the subject of several investigations. Sayers, Sayers, Liang and Long have shown a rapid decrease of the cholesterol and ascorbic acid of the adrenal gland in the rat and guinea pig, with a simultaneous production of increased quantities of liver glycogen, when adrenocorticotropic hormone is given. These decreases appear to take place only in the adrenal glands. Loewenstein and Zwenner reported the as yet unconfirmed isolation of an active cortical hormone containing the ascorbic acid moiety. McKee, Cobbey and Geiman reported that ascorbic acid-deficient guinea pigs show sluggishness in the rates of gluconeogenesis and glycogenolysis. Furthermore, the administration of cortical hormones to the vitamin-deficient guinea pigs does not stimulate production of liver glycogen as it does in normal guinea pigs. These results indicate an interesting relation between ascorbic acid and the activity of the adrenocortical hormone.

Other investigators have shown that in rats the concentrations of ascorbic acid and cholesterol parallel one another; i. e., a gland deficient in ascorbic acid is also deficient in cholesterol. These changes are in direct relation to the steroid output. It is believed by many biochemists that cholesterol is the precursor of the steroids.

When ACTH is administered, there is a fall in both the cholesterol and the ascorbic acid of the adrenal gland. With this drop there is a rise in the output of the cortical hormones. A similar result is seen when stress is applied, as in surgical shock.

Selye's work on the adaptation syndrome has shown that under conditions of stress, such as chronic infections, burns and peritonitis, there is a decrease in cortical lipid of the adrenal gland. These lipids, it is believed, are the adrenal cortex steroids. This decrease in cortical lipid is associated with a rise in urinary corticoids. All these findings by various investigators suggest a close relation of ascorbic acid, cholesterol and steroid hormones.

It is well established that hormones do not initiate new types of cellular activity but only influence the rate at which these functions proceed. Since it is now recognized that cellular function is based on underlying chemical transformations, it may be assumed that all any hormone does is either to facilitate or to retard certain types of chemical reactions within cells. It is postulated here that ascorbic acid is an integral part of this mechanism. Its proved relation to mesenchymal tissue, its known effect on capillary fragility, its role in oxidation-reduction processes and, finally, its high concentration in the adrenal gland, all serve to indicate an essential and basic role in the bony economy. It is interesting to note that when

ascorbic acid is given in massive doses to normal subjects there is a fall in total circulating eosinophils and lymphocytes, comparable to the effect of ACTH; a decrease of approximately 35 to 75 per cent in eosinophils results, together with lymphopenia.

Because of O'Connor's results in the treatment of collagen diseases, it was believed that ascorbic acid might be of value in the treatment of various ocular diseases. Ascorbic acid, in a routine dose of 5 Gm. a day by mouth for eight days, has been employed in the treatment of patients similar to the series covered in this paper. The results have been uniformly satisfactory in the cases studied to date. We, too, are of the opinion that the patients with involvement of the anterior segment do better than those with involvement of the posterior segment; we also believe that ascorbic acid is of great value in the treatment of postoperative cyclitis, dermatitis medicamentosa and the allergic conjunctivitides. It is suggested that ascorbic acid may be of value in the medical treatment of glaucoma and in the preoperative and postoperative management of surgical glaucoma. In these massive doses, there have been no signs of toxicity to ascorbic acid, and no subjective complaints have been offered or noted by the various patients.

The mode of action of ascorbic acid is as yet unknown. If cholesterol is degraded to the steroids, it must be by oxidative procedures. It is possible that by-products of this reaction may be toxic to the enzyme systems. Ascorbic acid, in view of its strong reducing properties, may play a role as a detoxifying agent.

This method of treatment is offered in the hope that others will employ it. Friedenwald's outstanding work on the physiology of the eye, particularly that aspect in which he considers ascorbic acid as the chief mediator of the oxidation-reduction mechanism, lends support to the belief that ascorbic acid is of value. It is suggested that its physiological mechanism should be studied in order that its position may be correlated with the use of ACTH and cortisone.

Dr. Seymour L. Cole, Los Angeles: In addition to the ocular diseases discussed by Dr. Olson in his excellent paper, cortisone and ACTH may be of use in treatment of exophthalmos. I tried cortisone in a case of exophthalmos of 20 years' duration following thyroidectomy for thyrotoxicosis. The patient had received every other form of treatment known, including use of diuretics, thyroid, and mixed steroid-hormone extracts, as well as irradiation of the pituitary gland, without effect. She had bilateral Naffziger decompression of the orbit, which still left a residual exophthalmos of 30 mm. before treatment with cortisone. After she had received 1 mg. of cortisone for six days, the Hertel exophthalmometer gave a reading of 22 mm. This was a reduction of 8 mm. in the exophthalmos in one week. In addition, the edema of the face completely disappeared. Since the therapy was given just one week before the meeting of this Session, I cannot give you the end result.

This case is significant, since cortisone is the first agent to produce any notable reduction of malignant exophthalmos.

Dr. J. A. Olson, Detroit: Several important points have been presented by the discussants. I should like to emphasize the importance of Dr. Swan's comments on the part ACTH and cortisone may play in delayed wound healing and in tissue atrophy. To date, we have had occasion to use both these agents immediately after operative procedures on the globe, and clinically we have been unable to note any deviation from the normal process of healing. However, more fundamental and detailed investigation is needed on this point. That tissue atrophy may occur from subcutaneously implanted cortisone pellets, or even by subconjunctival injection of cortisone, is conceivable; but our careful clinical observations on several patients who have been using cortisone topically as long as four months fail to reveal any evidence of changes in the corneal or conjunctival epithelium.

Dr. Cole has presented the case of a recently treated patient with malignant exophthalmos who has responded well to hormone therapy. The pathological picture of edema, lymphocytic infiltration and fibrosis of the retrobulbar structures

in this condition would lead one to anticipate a favorable response. However, because of the chronicity of a lesion of this type, one would also anticipate a recurrence on withdrawal of the hormone. We have had only one patient with malignant, or thyrotropic, exophthalmos under treatment and have found little or no response to intensive ACTH therapy.

I am unable to comment at any length on Dr. Cavanaugh's report on the ACTH-like effect of large doses of ascorbic acid, for the work is entirely new to me. His observations on the physiological responses to this therapy are interesting and appear to be worthy of more extensive investigation.

I should like to make an additional comment, directed principally to those clinical ophthalmologists who are undertaking investigative work in hormonal therapy. The field of endocrinology is broadening rapidly, and its ramifications into all fields of medicine are increasingly extensive. To those of us who find it difficult to keep abreast of the progress even in our own specialty, it would seem expedient to team with a well informed internist or endocrinologist when undertaking any investigations of ophthalmologic-hormonal therapy. We have found the guidance of the two endocrinologists working with us to be invaluable.

# ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE IN OPHTHALMOLOGY

## Report of Cases

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THE PURPOSE of this paper is to present preliminary clinical observations on the use of ACTH and cortisone when administered systemically and locally in the treatment of a variety of ocular lesions. The more important facts concerning the physiological effects of these hormones, beneficial and otherwise, which are essential for their clinical use are briefly reviewed. Excellent surveys of existing knowledge concerning their complex metabolic and therapeutic effects have been made available by Hench and associates,[1] Sprague and associates,[2] Mote [3] and the *Proceedings of the Staff Meetings of the Mayo Clinic* since April 1949. Some knowledge of the action of these potent hormones is important in helping to choose ocular conditions which might benefit from such therapy and likewise in recognizing and preventing toxic or otherwise undesirable manifestations.

### HISTORICAL SURVEY

In 1849 Addison demonstrated that the adrenal cortex was essential for life and showed that there was a difference between the action of the adrenal cortex and that of the adrenal medulla. In 1904 epinephrine was first isolated from the adrenal

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From the Department of Ophthalmology, Hospital of the University of Pennsylvania, the University of Pennsylvania School of Medicine and the Children's Hospital.

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2. Sprague, R. G., and others: Observations on the Physiologic Effects of Cortisone and ACTH in Man, Arch. Int. Med. **85**:199 (Feb.) 1950.

3. Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia. The Blakiston Company, 1950.

medulla, where it is produced. It was not until 1936 that Mason, Myers and Kendall,[4] in this country, simultaneously with Swiss investigators, identified cortisone (17-hydroxy-11-dehydrocorticosterone), or Kendall's compound E, which is secreted by the adrenal cortex. It was first synthesized in 1946 by Sarrett [5] and has recently been made available for clinical use by the combined efforts of the laboratories of Merck & Company, Inc., and Kendall and his associates at the Mayo Foundation.

In 1924 Herbert Evans [6] first reported that pituitary extract prevented the atrophy of the adrenal gland which results from the removal of the pituitary body in animals. The fraction which prevented this atrophy was adrenocorticotropic hormone (ACTH), first isolated in crude form by Collip in 1933.[6] It was later obtained in pure form through studies carried on in The Armour Laboratories by Koch and Hays, and others.[6] Thorn and his associates, in 1946,[7] first injected the substance in human beings and demonstrated that it stimulated the adrenal cortex. They pioneered the study of the metabolic effects in man with the administration of ACTH. Observations on the clinical effects of both cortisone and ACTH have been carried on more or less continuously since 1946.

## PHYSIOLOGICAL EFFECTS OF ACTH AND CORTISONE

ACTH and cortisone are only two small parts of the complicated endocrine-hormone system of the body. The anterior lobe of the pituitary is in many ways the "master gland" of the endocrine system but is, at least partially, under control of the hypothalamus, probably through some, as yet, unidentified hormone (fig. 1). The anterior lobe of the pituitary secretes several hormones which activate the endocrine system of the body. These include the gonadotropic, thyrotropic, parathyrotropic, pancreaticotropic, lactogenic, diabetogenic and adrenotropic, or adrenocorticotropic, hormones. Adrenocorticotropic hormone, abbreviated as ACTH, is liberated into the circulation and exerts a stimulating effect on the adrenal cortex. When thus stimulated, the adrenal cortex secretes about 30 hormones, which chemically are steroids. They exert a profound effect on regulating a variety of metabolic processes and are classified into three main groups, depending on the predominant effect.

Group 1, in which cortisone, or Kendall's compound E, is included, affects chiefly carbohydrate and protein metabolism. An important function of this group of hormones appears to be that of increasing the resistance of the organism to certain forms of stress, for example, exposure to cold, starvation and physical

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exertion. They tend to produce a negative nitrogen balance and an increased excretion of potassium, phosphate, calcium and chloride, possibly through lowering the renal threshold to these substances. The formation of glucose and glycogen from noncarbohydrate sources is increased. A relatively insulin-resistant hyperglycemia may result, which unmasks latent diabetes. Normal persons have an adequate pancreatic reserve to care for the increased insulin resistance. These properties can produce undesirable effects during treatment with ACTH or cortisone.

Group 2 contains desoxycorticosterone and other steroids. These substances are particularly concerned with salt and water metabolism and are important in maintaining life in the adrenalectomized animal, owing to their effects on electrolyte

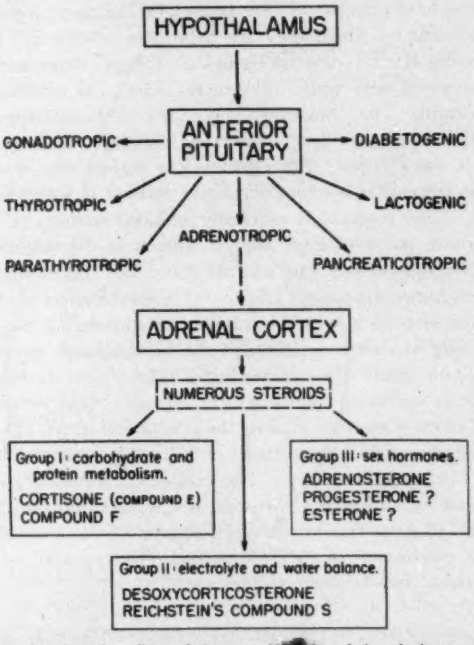


Fig. 1.—Diagram showing the effect of the anterior lobe of the pituitary gland on the adrenal cortex.

balance. They cause retention of sodium and chloride with concurrent retention of fluids and diminished perspiration.

Although the effects of the adrenocortical hormones of group 1 and group 2 are somewhat separate, each also has some of the effects of the other, although to a slighter extent. For example, cortisone and the hormones of group 1, although predominantly affecting protein and carbohydrate metabolism, do have a definite, though weaker, effect on electrolyte and water balance. The reverse is true of the hormones of group 2.

A third group is essentially the sex hormones. These cortical sex hormones are at least partially responsible for secondary sex characteristics. They influence the

growth and distribution of pubic and axillary hair and the growth of hair on the extremities. The physiological effects obtained by administering ACTH and cortisone are similar but not identical. ACTH causes an increased output of all the hormones of the adrenal cortex and therefore has a much more widespread effect on body metabolism than cortisone given alone. Cortisone produces, chiefly, the effects of the steroids of group 1 and exerts only a slight influence on salt and water metabolism.

ACTH and cortisone have nearly the same effect on most disease processes for which they have been used, the exception being that ACTH is ineffective if the adrenal cortex has undergone atrophy, as in Addison's disease. Cortisone, on the other hand, acts as substitution therapy, replacing adrenal cortex function. ACTH and cortisone have been effective chiefly against the collagen degeneration diseases. The exact mechanism by which they are helpful is unknown. They possess the ability of depressing the response of tissues to allergic states and of blocking the effect of inflammatory and toxic substances, which in ophthalmology may be particularly important. They, however, do not alter the underlying allergic state, for once treatment is stopped the allergy continues unchanged and the tissues are again able to respond to the allergen. For example, the patient who is strongly sensitive to tuberculin may respond in a strongly positive manner to a cutaneous test prior to ACTH therapy. This reaction is markedly reduced during ACTH or cortisone therapy but becomes positive again after treatment is discontinued.

A close relationship between the adrenal gland and the pituitary is maintained through a complex hormonal control (fig. 2). Under the effect of stress, the adrenal medulla secretes epinephrine, which is capable of stimulating the anterior lobe of the pituitary directly or indirectly, through the hypothalamic nuclei. The anterior lobe of the pituitary gland then secretes ACTH, which stimulates the adrenal cortex to produce an increased number of the adrenocortical steroids. An increase in the blood level of these steroids inhibits the production of ACTH by the pituitary. On the other hand, diminished blood levels of cortical steroids result in an increased liberation of ACTH by the pituitary. The exogenous administration of ACTH or adrenocortical hormones, of which cortisone is one, interferes with this cycle in a similar way. ACTH gives rise to increased activity of the adrenal cortex. Cortisone inhibits the production of ACTH by the pituitary and substitutes for the adrenal cortex, which then becomes trophic.

## ADMINISTRATION OF ACTH AND CORTISONE

### A. Parenteral Administration

ACTH is extracted from the anterior lobe of the pituitary gland of hogs. Cortisone, on the other hand, is available in synthetic form in sufficient quantities for clinical use. Both drugs are given subcutaneously. The effect of subcutaneously administered ACTH lasts about six hours. The substance should therefore be given at six hour intervals. Cortisone, on the other hand, has a more prolonged action and is best given in a single daily dose. The average dose of ACTH for children is about 10 mg. four times a day. For premature infants the initial dose of 1 mg. should be repeated four times a day. This dose can be gradually increased, so that the child or infant finally receives as high as 10 mg. four times a day. For adults the usual dose of ACTH is 20 to 50 mg. four times a day, depending on the therapeutic response. Cortisone is usually given in one injection of 100 mg. daily.

The dose for small infants and children is as yet unestablished. However, the dose may be as high for infants as for adults, depending on the severity of the disease being treated. Calculation of the dose for infants and children depends, therefore, not on the body weight but, rather, on the therapeutic response required in treating the disease. With both drugs withdrawal symptoms may occur when the drug is discontinued, owing to depression of the anterior lobe of the pituitary by ACTH or of the adrenal cortex by cortisone. This response is usually not serious and may be avoided to a great extent by gradually decreasing the dose during the last few days of treatment.

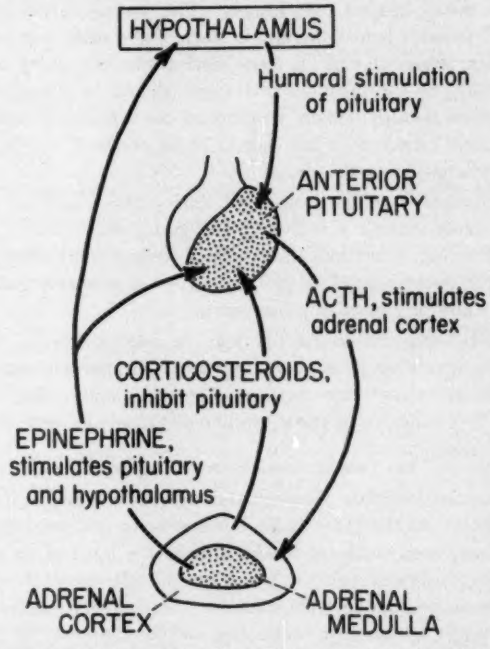


Fig 2.—Diagram showing the complex interrelationship of the hypothalamus, the anterior lobe of the pituitary body and the adrenal glands.

The toxic manifestations of the substances are essentially the same. Pulmonary edema and water retention are more commonly seen with ACTH than with cortisone because cortisone is not primarily concerned in electrolyte balance and water retention. Hypertension is a rather rare toxic manifestation which may be seen with both drugs. It had been thought in the past that diabetes could be produced by cortisone or ACTH, but the consensus now is that this is not true. Instead, a latent diabetes may be unmasked by either drug. The drugs produce an insulin-resistant state, which is taken care of in nondiabetic subjects by the normal pancreatic reserve. In persons with latent diabetes, there is an inadequate pancreatic reserve, and the diabetes is made clinically evident. If either drug is given to the known diabetic, the

insulin requirements are greatly increased. With either drug, certain cutaneous signs may appear, which include acneform and pustular eruption and dermatological manifestations of Cushing's syndrome, that is, pigmented striae and an increase in axillary and pubic hair and in other body hair. Acneform and pustular eruptions of the skin occur less frequently with cortisone than with ACTH. It is believed that a condition resembling the Cushing syndrome, including obesity and rounding of facial contours, may occur during treatment with either drug.

When the drugs were first used clinically, numerous laboratory studies were made in an effort to determine the therapeutic effect of the drugs and to foresee toxic manifestations. However, a few simple clinical tests can be done which will be adequate to guard against overdosage. The fasting blood sugar should be estimated for all patients before therapy is started, and daily determinations of the afternoon urinary sugar, should be made during the first three or four days of therapy. Estimates of the fasting blood sugar should be repeated several times during the course of therapy. Daily weight and blood pressure readings should be made to detect fluid retention or increase in blood pressure, which might serve as indications for discontinuing the drug.

Emotional changes have been observed during the course of treatment with either drug. Usually there is a feeling of well-being, which may approach a state of euphoria. However, sometimes there may be severe depression, particularly on withdrawal of the substance. Use of these drugs is probably contraindicated in frank psychotic states or clinical psychoneurosis.

The therapeutic response to ACTH may be followed by a reduction in the eosinophil count, which drops to very low levels, frequently zero. This is an unreliable indication in cortisone therapy. The therapeutic effect of cortisone is empirical and is best indicated by the subjective and objective signs of improvement.

### B. Topical Application of Cortisone

Since ACTH must stimulate the adrenal cortex to be effective, it cannot be used topically. Cortisone, on the other hand, since it is an end product, may be used topically. We have used cortisone locally only in the form of drops. One cubic centimeter of the cortisone suspension, which contains 25 mg. of the drug, is diluted with 5 cc. of isotonic sodium chloride solution. This amount provides about seven to 10 days' treatment for one eye, depending on the frequency of administration. In the acute state 1 drop is used every hour while the patient is awake. In the subacute stage 1 drop is used five times a day; in the maintenance stage, 1 drop is instilled three times a day.

Cortisone is also given subconjunctivally, a route with which we have had no experience.

## REPORT ON PATIENTS WITH OCULAR CONDITIONS TREATED WITH CORTISONE AND ACTH

Reports on the use of cortisone and ACTH in the treatment of ocular disease are beginning to appear in the ophthalmologic literature.[8] These substances offer

8. Woods, A. C.: Clinical and Experimental Observation on the Use of ACTH and Cortisone in Ocular Inflammatory Disease, Am. J. Ophth. **33**:1325, 1950. Mann, W. A., and Markson, D. E.: A Case of Recurrent Iritis and Episcleritis on a Rheumatic Basis Treated

considerable promise in ocular therapeutics, apparently being of benefit in many previously intractable conditions, especially those which result from anaphylactic or allergic reactions. Among these are endophthalmitis phacoanaphylactica, syphilitic interstitial keratitis and sympathetic ophthalmia. Iridocyclitis and uveitis, on the basis of focal response or bacterial allergy, are also accepted entities. The relation of ocular disease to arthritic involvement and other collagen diseases is also recognized. Furthermore, the eye seems to be an ideal structure for treatment with topical applications of cortisone, for it offers the advantage of continuing treatment over long periods without the danger of systemic effects.

TABLE 1.—*Ocular Conditions Treated with Systemic Cortisone or ACTH*

| Case No. | Diagnosis | Eye | Age, Yr. | Sex | ACTH or Cortisone, Mg. | Days Treated | Condition at End of Treatment |
|---|---|---|---|---|---|---|---|
| 1 | Focal choroiditis | OD | 21 | M | C 1,300 | 11 | Improvement |
| 2 | Focal choroiditis | OD | 28 | M | C 1,600 | 14 | Improvement |
| 3 | Focal choroiditis | OU | 30 | F | C 1,675 | 16 | Improvement |
| 4 | Focal choroiditis | OD | 18 | F | A 440 | 10 | Marked improvement |
| 5 | Focal choroiditis | OU | 7 | F | A 245 | 6 | No definite improvement |
| 6 | Focal choroiditis | OS | 4 | M | A 550 | 10 | No definite improvement |
| 7 | Diffuse granulomatous uveitis, chronic | OD | 31 | M | C 900<br>A 90 | 12 | No definite improvement |
| 8 | Diffuse granulomatous uveitis, chronic | OU | 8 | M | C 1,190 | 19 | No improvement |
| 9 | Diffuse granulomatous uveitis, chronic | OD | 28 | M | C 2,100 | 31 | Vitreous cleared |
| 10 | Diffuse granulomatous uveitis, chronic | OU | 42 | F | C 1,450<br>A 70 | 14 | Inflammatory signs subsided |
| 11 | Interstitial keratitis | OU | 3 | M | A 325 | 7 | Rapid improvement |
| 12 | Interstitial keratitis | OD | 15 | F | A 500 | 7 | Rapid improvement |
| 13 | Interstitial keratitis | OU | 9 | F | A 747.5 | 20 | No definite improvement |
| 14 | Acute nongranulomatous uveitis | OU | 39 | F | C 1,000 | 11 | Complete remission |
| 15 | Harada's disease | OU | 18 | F | C 900 | 12 | No improvement |
| 16 | Still's disease; band keratitis | OU | 18 | F | C 920 | 12 | No improvement |
| 17 | Phacoanaphylaxis | OD | 76 | M | C 3,300 | 41 | Improvement |
| 18 | Optic neuritis | OU | 25 | M | A 1,300 | 21 | Questionable improvement |
| 19 | Optic neuritis | OS | 40 | M | A 420 | 11 | Questionable improvement |
| 20 | Retrobulbar neuritis | OS | 21 | M | A 326 | 11 | Questionable improvement |
| 21 | Retrobulbar neuritis | OS | 34 | M | C 1,025 | 12 | Questionable improvement |
| 22 | Angiospastic retinopathy | OU | 31 | M | C 900 | 7 | No improvement |
| 23 | Angiospastic retinopathy | OU | 43 | M | C 1,000 | 7 | No improvement |
| 24 | Retrolental fibroplasia | OU | 10 wk. | M | A 112 | 14 | Arrested |
| 25 | Retrolental fibroplasia | OU | 7 wk. | F | A 238.5 | 18 | Questionable improvement |
| 26 | Retrolental fibroplasia | OU | 3 wk. | M | A 0.5 | 1 | Questionable improvement |
| 27 | Retrolental fibroplasia | OU | 5 mo. | M | A 420 | 26 | Arrested |
| 28 | Retrolental fibroplasia | OU | 3 mo. | F | A 267 | 21 | No improvement |
| 29 | Tay-Sachs disease | OU | 1 | F | A 968 | 41 | No improvement |
| 30 | Thyrotoxic exophthalmos | OU | 56 | F | A 320 | 7 | No improvement |

### A. Ocular Conditions Treated with Systemically Administered Cortisone or ACTH

We have treated 36 patients (55 eyes) having a rather wide variety of ocular lesions by systemic administration of cortisone or ACTH. Because of the numbers

with ACTH, ibid. **33**:459, 1950. Olson, J. A.; Steffensen, E. H.; Margulis, R. R.; Smith, R. W., and Whitney, E. L.: Effect of ACTH on Certain Inflammatory Diseases of the Eye, J. A. M. A. **142**:1276 (April 22) 1950. Steffensen, E. H.; Olson, J. A.; Margulis, A. R.; Smith, R. W., and Whitney, E. L.: Cortisone in Inflammatory Eye Disease, Am. J. Ophth. **33**:1033, 1950. Gordon, D. M., and McLean, J. M.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy in Ophthalmologic Conditions, J. A. M. A. **142**:1271 (April 22) 1950. Blake, E. M.; Fasanella, R. M., and Wong, A. S.: The Effect of ACTH in Glaucoma, Am. J. Ophth. **33**:1231, 1950.

of patients treated, space will not permit the report of individual cases. The cases will, therefore, be discussed in various groups according to the type of disease.

1. *Focal Choroiditis.*—Six patients having focal choroiditis were treated by parenteral injections, three of ACTH and three of cortisone. Four of the six patients had fresh focal lesions, whereas two (patients 5 and 6) had lesions of several weeks' duration. The lesions were nonspecific except in cases in which the tuberculin test elicited a strongly positive reaction.

All the patients with fresh lesions seemed to benefit from treatment. The local exudative phenomenon disappeared in 10 days to two weeks, instead of requiring several weeks, as frequently occurs. The course of the lesions in the two patients with chronic lesions appeared unaltered.

The results of treatment of this disease were encouraging.

2. *Chronic Diffuse Granulomatous Uveitis.*—Only four patients having chronic diffuse granulomatous uveitis were treated, and all responded poorly. The disease was nonspecific in all but patient 7, in whom tuberculin sensitivity was found. Before treatment all patients showed numerous keratic precipitates, an aqueous flare and pronounced clouding of the vitreous, but no discrete choroidal lesions. The patient who was sensitive to tuberculin showed no improvement at the end of 12 days of ACTH therapy. Patients 8 and 9 showed probable slight clearing of the vitreous, but the retinal edema persisted and engorgement of the retinal vessels remained unchanged. Patient 10 showed inflammatory signs at the start of treatment, and, although these subsided to a striking degree with ACTH, the basic inflammatory process continued unabated. There was also rapid development of intumescent cataractous changes in a previously clear lens. This condition was not observed in any of the other patients in our series.

The patients showed no improvement as a result of treatment.

3. *Syphilitic Interstitial Keratitis.*—Three patients having syphilitic interstitial keratitis were treated systemically with ACTH. Patient 11, who was 3 years of age, presented classic signs of bilateral early acute interstitial keratitis, manifest by clouding of the deep layers of the cornea with beginning deep corneal vascularization. The corneas completely cleared, and his eyes became white after one week of therapy.

Patient 12 had received penicillin and fever therapy for bilateral interstitial keratitis several months previously. Because of a flare-up in her right eye, with several discrete areas of deep opacity and characteristic vascularization of the right cornea, as well as a small number of keratic precipitates, ACTH therapy was started. Her eye became white before the termination of a week of treatment, and the opacities had cleared rather remarkably. She has had no recurrence in over one year of observation.

Patient 13, a 9 year old Negro girl, presented the signs of severe advanced interstitial keratitis with the "salmon patch" type of corneal vascularization. No noticeable improvement resulted from ACTH therapy. A total of 20 days of therapy was given, in two courses. Similar changes had subsequently developed in the second eye, but she showed no response to local use of cortisone.

The results in treatment of this condition were encouraging.

4. *Miscellaneous Types of Uveitis.*—A patient having bilateral severe acute diffuse nongranulomatous uveitis of undetermined cause was treated with cortisone, with complete remission of the disease. Prior to cortisone therapy she showed severe ciliary injection with marked iridocyclitis, clouding of the vitreous and edema of the disk in each eye. All these signs disappeared during the first week of therapy, except for edema of the disk, which had not cleared at the end of three months. No central scotomas were detected.

A patient with all the classic signs of severe acute Harada's disease did not respond to treatment. An 18 year old girl with Still's disease (multiple rheumatoid arthritis), having had arthritis with bilateral uveitis since 2 years of age, was treated with ACTH, without improvement. This is probably not surprising in view of the duration of her signs and symptoms, the presence of a band-shaped corneal opacity, an extensive posterior synechia and complicated cataractous changes. A patient with severe endophthalmitis phacoanaphylactica was treated with two courses of systemically administered cortisone, over a total period of 41 days, in addition to which cortisone drops were instilled locally. Marked improvement

occurred after each course of systemic therapy, but the condition did not subside until the lens material was removed. After removal of the lens and topical application of cortisone, inflammatory signs cleared.

5. *Optic and Retrobulbar Neuritis.*—Four patients showing characteristic signs of optic or retrobulbar neuritis were treated. The response to therapy was extremely difficult to evaluate because of the notoriously unpredictable course of demyelinating diseases. All the patients showed a tendency to improve, but for none were the findings sufficiently dramatic to warrant favorable evaluation. Three of the patients (18, 20 and 21) seemed to fall in the category of multiple sclerosis. The fourth (patient 19) had onset of optic neuritis five days after vaccination for smallpox. His response was the least favorable. The visual acuity in his affected eye improved from 6/60, before treatment, to 6/20 after a course of treatment of 11 days. Secondary optic nerve atrophy ensued.

The results were questionable.

6. *Angiospastic Retinopathy.*—Two patients with signs typical of angiospastic retinopathy were treated. Neither showed evidence of improvement.

Treatment failed to effect improvement in this condition.

7. *Retrolental Fibroplasia.*—Five patients were treated for retrolental fibroplasia. For only two of the patients were the data of value in judging the effects of ACTH on the disease. Patient 25 died before final evaluation could be made. Patient 26 received an insufficient amount of ACTH, only 0.5 mg., and patient 27 was so old when treatment was started that the disease had probably become spontaneously arrested. The result in patient 24 was sufficiently encouraging, however, that we feel the treatment should be given further trial.

PATIENT 24.—*Baby B. A., born April 11, 1950. Period of gestation, 34 weeks. Weight at birth, 1,860 Gm. Diagnosis, bilateral retrolental fibroplasia. Treatment, systemic administration of ACTH.*

This patient was first examined on April 28, 1950, 17 days after birth. On the first examination the fundi appeared normal except for an arteriovenous ratio of 1:2, which is not unusual for premature infants. On May 5 the right eye showed hazy vitreous over the central portion of the disk. The arteries showed extreme engorgement and tortuosity, and there was a retinal detachment nasally. The left eye was similar except that no detachment was seen. On May 6 there was extension of the detachment in the right eye. ACTH therapy was started, 2 mg. being given every six hours. On May 9 the left eye showed peripheral elevation of the retina. On May 11 the only significant change was some clearing of the vitreous. On May 16 no detachment could be observed in either eye. The retinal vessels were slightly less engorged. On May 19 ACTH was discontinued. The patient was discharged on May 25, and followed as an outpatient. Progressive improvement was noted, and on the last visit the ocular fundi were normal.

PATIENT 25.—*Baby L. L., born Nov. 7, 1949. Gestation period, 23 weeks. Weight at birth, 945 Gm. Date of first examination, December 30, at age of 53 days. Diagnosis, bilateral retrolental fibroplasia. Treatment, 228.5 mg. of ACTH. Period of treatment, 13 days.*

This premature infant was the surviving member of twins. The only known cause of prematurity was premature rupture of the membranes. She was first examined 53 days after birth, since prior to this time she had been in an incubator. Initial examination showed bilaterally dilated and tortuous retinal veins. On January 5 the right eye showed fibrous tissue with elevation in the temporal periphery of the retina. The left eye showed no change. On January 7 there were progression in the size of the retinal vessels and an increase in the extent of the retinal detachment, with prominent extension of fibrous tissue out toward the extreme periphery of the globe. There were one or two hemorrhages. The left eye showed no significant change. On January 7 treatment with ACTH was started. During treatment with this substance the course of the disease was not altered, and a congenital retinal fold went on to develop in the right eye. During the treatment the left eye showed increased tortuosity in the veins and scattered retinal hemorrhages with elevation of the retina from 10 to 7 o'clock. A discrete area of fibrous tissue could not be seen, as in the right eye.

The child presented many complications during her postnatal course. During ACTH therapy there developed a generalized pustular eruption, secondary anemia, pneumonia and a

simple fracture of the left femur. This was followed by exfoliative dermatitis. The infant died on February 27, the immediate cause of death being bronchopneumonia which did not respond to antibiotics. It is suspected that poisoning due to ACTH was also a factor.

PATIENT 26.—*Baby L. D., born Jan. 24, 1950. Gestation period 32 weeks. Weight at birth 1,660 Gm. Diagnosis, bilateral retrolental fibroplasia. Treatment, ACTH, 0.5 mg.*

This premature infant received 0.5 mg. of ACTH in a single dose shortly after birth. The therapy was discontinued because the baby seemed somewhat moribund, due to pneumonitis. The infant was first examined on January 31, at which time there was tremendous engorgement of the vessels of the right eye. The arteries and the veins appeared to anastomose, a condition at first thought to be von Hippel's disease (angiomatosis retinae). Similar changes in the left eye followed those in the right eye by one week to ten days. During the course of the next month the process slowly subsided, without evidence of retinal detachment, and by March 7 the appearance of the fundus was normal in both eyes. It was believed that this was a spontaneous remission of retrolental fibroplasia and did not represent a therapeutic result of treatment with ACTH.

PATIENT 27.—*Baby V. M. Diagnosis, bilateral retrolental fibroplasia. Age at beginning of treatment, 5 months. Total dose of ACTH, 420 mg., in 26 days.*

When first seen, the child showed vascular engorgement of the right eye, with elevation of the retina in the periphery above and below. The left eye showed advanced changes due to retrolental fibroplasia, which included extensive retinal detachment. The child was treated with ACTH at Lankenau Hospital, and apparently the disease was arrested in the right eye. The left eye showed no improvement.

PATIENT 28.—*Baby M. W., born Feb. 12, 1950. Weight at birth, 1,000 Gm. Diagnosis, bilateral retrolental fibroplasia. Treatment, ACTH, 267.5 mg., in 2 days, by intramuscular injection.*

This premature infant was delivered by cesarean section at the end of 26 weeks' gestation. She was first seen on April 26, 1950, through the courtesy of Dr. Fred Frisch. At that time there were bilateral retinal detachments, tortuous blood vessels, vitreous haze and disorganization of the optic disk. The eyes presented essentially the same picture. The detachments were first noted 72 days after birth. The patient was admitted to Children's Hospital, and on April 29 ACTH therapy was started, in a dosage of 2.5 mg. every six hours, or 10 mg. daily. Although there was a prompt drop of eosinophils to 50 per cent, the patient's condition did not improve. Therefore, on May 3 the dose of ACTH was increased to 5 mg. every six hours, or 20 mg. daily. On May 12 administration of the ACTH was tapered off and was finally discontinued on May 19.

During the course of treatment, both eyes became steadily worse, until complete retinal membranes were formed behind the lens. While under treatment with ACTH the patient simultaneously received vitamins C, D and E.

8. *Infantile Amaurotic Familial Idiocy.*—A girl 1 year of age, who presented the classic clinical picture of infantile amaurotic familial idiocy (Tay-Sach disease), was followed through the courtesy of Dr. John Stokes, Children's Hospital, Philadelphia, and was treated for a period of 41 days, a total of 968 mg. of ACTH being administered. No ocular improvement was observed, but Dr. Stokes gained the impression that progression of the disease was somewhat slowed.

9. *Thyrotropic Exophthalmos.*—A patient presenting early signs of thyrotropic exophthalmos was treated with ACTH for seven days. No improvement resulted.

### B. OCULAR CONDITIONS TREATED WITH CORTISONE APPLIED TOPICALLY

Cortisone, applied topically, was used in the treatment of 68 eyes with various types of ocular lesions. The best results occurred in lesions of the anterior segment of the eye, and at times the response was phenomenal.

1. *Anterior Uveitis.*—(*a*) Acute Nongranulomatous Uveitis or Iridocyclitis: Three patients were treated for acute iridocyclitis, with complete remissions occurring in 48 to 72 hours. Evaluation of treatment on the basis of so few eyes is difficult in view of the unpredictable course which this disease takes.

The results of treatment were encouraging.

(*b*) Endophthalmitis Phacoanaphylactica: A patient with endophthalmitis phacoanaphylactica is included in this series because, even though he had had two courses of cortisone administered systemically, the condition seemed to be considerably helped by local cortisone therapy. When no treatment was given, the eye would show signs of inflammation, which again subsided after instillations of cortisone.

The results were encouraging.

(*c*) Retained Lens Material After Attempted Intracapsular Extraction: Two patients were treated because of persistent iridocyclitis due to retained lens material after attempted intracapsular cataract extractions. Both showed signs of iridocyclitis, one presenting large numbers of keratic precipitates. Both eyes became white and quiet within four to seven days after the institution of treatment. Use of cortisone was continued for three weeks to two months. No relapse occurred.

The results were encouraging.

TABLE 2.—*Patients Treated with Local Instillation of Cortisone in Form of Drops*

| Diagnosis | Subtype | No. of Eyes Treated | Result | | |
|---|---|---|---|---|---|
| | | | Remission | Improvement | No Improvement |
| Anterior uveitis | | | | | |
| | Acute nongranulomatous | 3 | 3 | .. | .. |
| | Endophthalmitis phacoanaphylactica | 1 | .. | 1 | .. |
| | Retained lens material | 2 | 2 | .. | .. |
| Posterior uveitis | | | | | |
| | Granulomatous | 12 | .. | .. | 12 |
| | Harada's disease | 2 | .. | .. | 2 |
| | Vogt-Koyanagi syndrome | 1 | .. | .. | 1 |
| Keratitis | | | | | |
| | Syphilitic interstitial | 2 | 2 | .. | .. |
| | Metaherpetica | 2 | 1 | 1 | .. |
| | Sclerosing | 1 | .. | 1 | .. |
| | Profunda | 1 | 1 | .. | .. |
| | Superficial punctate | 2 | 2 | .. | .. |
| | Mustard gas | 2 | .. | .. | 2 |
| | Nonspecific marginal | 6 | 5 | 1 | .. |
| | Keratouveitis, cause undetermined | 3 | .. | 3 | .. |
| Keratoconjunctivitis | | | | | |
| | Chronic Staphylococcus sensitivity | 5 | 3 | 2 | .. |
| | Phlyctenular | 3 | 2 | 1 | .. |
| | Stevens-Johnson disease | 4 | .. | .. | 4 |
| Blepharoconjunctivitis | | 8 | 4 | 4 | .. |
| Vernal conjunctivitis | | 6 | 6 | .. | .. |
| Episcleritis | | 3 | 3 | .. | .. |
| | | 69 | 34 | 14 | 21 |

2. *Posterior Uveitis.*—Chronic granulomatous posterior uveitis without focal choroidal lesions was treated in 12 eyes, without improvement. Treatment was continued for one to several months, the drops being given at two hour intervals. A patient who had Harada's disease, with bilateral uveitis, was treated without success with local instillations of cortisone, after a systemic course of the same hormone. A patient who presented signs of the Vogt-Koyanagi syndrome of long duration showed no improvement with local cortisone therapy.

This treatment produced no improvement in the condition.

3. *Keratitis.*—Keratitis of several types was treated. The results were often extremely gratifying.

(*a*) Syphilitic Interstitial Keratitis: Both eyes of a patient presenting the typical signs of syphilitic interstitial keratitis were treated with topical applications of cortisone, instilled at two hour intervals. The infiltrate involved the deep layers of most of the lower half of the cornea of the left eye and the lower periphery of the cornea of the right eye. Symptoms had been present about one week at the time treatment was started. Response to cortisone therapy was dramatic, the eyes becoming white and the opacities clearing at the end of two weeks. No other treatment was given except atropine.

The results were encouraging.

(*b*) Keratitis Metaherpetica: Two eyes with keratitis metaherpetica were treated with local applications of cortisone. The first patient had had recurrent symptoms after an attack of dendritic keratitis one year previously. A complete remission resulted, and the condition has not recurred in the two months following therapy.

The second patient had had recurrent symptoms for several years. The present attack was of two months' duration. She showed improvement of symptoms, the eye previously inflamed becoming white, but the erosion showed no signs of healing.

The results of treatment were questionable.

(*c*) Sclerosing Keratitis: Only one eye with sclerosing keratitis was treated. A typical wedge-shaped infiltrate, showing deep vascularization extended into the lower nasal quadrant of the cornea of the left eye. Tuberculin allergy was pronounced. Symptoms subsided during the first four days of treatment, and the opacity gradually cleared during the following month, with simultaneous regression of the vessels. Recurrence has not taken place in two months following cessation of therapy.

The therapeutic results were encouraging.

(*d*) Keratitis Profunda: One eye showing the deep localized corneal infiltrates suggestive of keratitis profunda was treated. The etiologic agent was unknown. Complete remission occurred, beginning within 48 hours after the start of treatment. Follow-up observation has been inadequate.

The results were encouraging.

(*e*) Superficial Punctate Keratitis: Superficial punctate keratitis was encountered in two eyes. The duration of the disease in one eye was known to be 16 months, and that in the other eye, of another patient, was at least two years. All previous therapy had failed. The etiologic agent was unknown. The corneas appeared completely healed within four days after cortisone therapy. Cortisone was continued with one patient. No flare-up occurred in this eye. Recurrence was noted in the other within four days after cessation of treatment, whereupon cortisone therapy was once more instituted and clearing again occurred.

The results were encouraging.

(*f*) Mustard Gas Keratitis: Two eyes showing progressive changes of mustard gas (2-chloroethyl sulfide) keratitis were treated with topical applications of cortisone. No improvement was noted. The mustard gas injury had been incurred in 1944.

Cortisone did not produce improvement in this condition.

(*g*) Nonspecific Marginal Keratitis: The most dramatic results obtained from topical use of cortisone were found in the treatment of nonspecific marginal keratitis. Five of six eyes with this condition showed complete remission, improvement beginning within a few hours after instillation of the drops. The patients usually stated that their symptoms cleared after the second or third instillation. In one eye, slow improvement occurred over a period of many weeks, but the lesion was of long duration and heavily vascularized, and a therapeutic conjunctival flap had previously been drawn.

The results were encouraging.

(*h*) Keratouveitis: Three patients were treated who had rather pronounced corneal changes secondary to uveitis. They are placed in this category because of the corneal manifestations, as well as the severe ciliary injection. In each instance the inflammatory signs were much improved by topical instillation of cortisone, but the underlying process continued. Considerable corneal clearing occurred.

The results were questionable.

4. *Keratoconjunctivitis.*—(*a*) Chronic Keratoconjunctivitis Associated with Staphylococcus Sensitivity: Long-standing, recurrent keratoconjunctivitis associated with sensitivity to Staphylococcus was found in five eyes. All the patients had had the usual bacteriologic studies and various accepted types of treatment. Complete remission of the corneal and conjunctival changes occurred in three eyes within one to two weeks after onset of cortisone therapy. Two were improved, the condition flaring up when treatment was stopped.

The results were encouraging.

(*b*) Phlyctenular Keratoconjunctivitis: Lesions attributed to phlyctenular keratoconjunctivitis were found in three eyes. Remissions occurred in two of the eyes. In one eye the inflammatory signs improved. Evaluation of the treatment was impossible.

The results were encouraging.

(*c*) Stevens-Johnson Disease: Ocular sequelae, or Stevens-Johnson disease with corneal scarring and shrinkage of the conjunctiva, were treated in four eyes of two patients. As might have been predicted, the course of the disease was uninfluenced.

The treatment resulted in no improvement.

5. *Blepharoconjunctivitis.*—Blepharoconjunctivitis, probably due to staphylococcus allergy, was treated in eight eyes, complete remission occurring in four and improvement being found in the other four. Cortisone therapy is being continued.

The results are encouraging.

6. *Vernal Conjunctivitis (Atypical).*—Atypical conjunctivitis of the type seen at the height of the pollen season was treated in six eyes. Each eye had circumcorneal injection with small translucent follicles at the perilimbal region. Response to cortisone was pronounced, complete remission being produced in 44 to 72 hours. Follow-up observation has revealed only one recurrence, which again responded promptly to cortisone. No patients with classic vernal conjunctivitis involving the upper lids with pigment-like follicles were treated.

The results were encouraging.

TABLE 3.—*Effect of ACTH and Cortisone in Keratoplasty*

| No. | Diagnosis | Prognosis Group | Age | Sex | Drug | Dose, Mg. | Route | Days Treated | Result |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Rosacea keratitis | IV | 64 | M | Cortisone | 1,400 | Systemic | 12 | Failure |
| 2 | Lymphogranuloma venereum keratitis | IV | 37 | F | ACTH | 840 | Systemic | 10 | Failure |
| 3 | Keratoconus | I | 18 | F | ACTH | 1,100 | Systemic | 15 | Clear graft |
| 4 | Adherent leukoma | III | 37 | M | ACTH | 850 | Systemic | 12 | Clear graft |
| 5 | Interstitial keratitis | IV | 37 | M | ACTH | 620 | Systemic | 10 | Failure |
| 6 | Traumatic leukoma | III | 33 | M | Cortisone | 470<br>75 | Systemic and local | 5<br>21 | Clear graft |
| 7 | Healed staphylococcic keratitis | II | 45 | F | Cortisone | 50 | Local | 14 | Clear graft |
| 8 | Corneal ulcer (therapeutic transplant) | IV | 57 | M | Cortisone | 125 | Local | 60 | Clear graft |
| 9 | Keratoconus | III | 33 | M | Cortisone | 100 | Local | 30 | Clear graft |

7. *Episcleritis.*—Episcleritis of undetermined cause was reported in three eyes. Prompt remission occurred within two to four days in all instances. Because of the transient nature of this condition, evaluation of the treatment is impossible.

The results are encouraging.

### C. Effect of ACTH and Cortisone in Keratoplasty

ACTH and cortisone were used postoperatively in a number of patients who had had keratoplasty. ACTH was given parenterally only, but cortisone was used locally as well. It was felt that opacification and vascularization of transplanted corneal tissue probably result from an intolerance of the recipient eye to the donor tissue. If this were on an allergy-antibody basis, there would be reason to believe that ACTH or cortisone might be helpful.

A total of nine patients were treated with ACTH or cortisone postoperatively after corneal transplantation. The first five received systemic therapy, and the sixth received a combination of systemic and local treatment. The last three received only topical applications of cortisone. Therapy was instituted for all patients during the latter part of the second to the fifth postoperative week, a time when the eye appears irritable, the graft begins to haze and vessels show a tendency to invade the transplant. Such a sequence of events occurs in most eyes after corneal transplantation and is worst in badly scarred eyes, which have the poorest prognosis. The eyes to receive grafts have therefore been graded I to IV as suggested by Castroviejo, group I having the best and group IV the poorest prognosis.

The first patient had had three previous keratoplasties, the cornea of his eye being entirely opaque and placed in group IV. Cortisone, given over a period of 12 days, did not alter the course of the reaction, the graft becoming totally vascularized and opaque.

The second patient (prognostic group IV) had had one previous unsuccessful corneal transplantation. ACTH was given systemically, beginning on the sixteenth postoperative day. Not only did the ocular reaction to the graft continue, but the wound broke down, permitting prolapse of the iris and precipitating a sequence of events which eventually necessitated removing the eye.

The third patient (prognostic group I) was operated on because of keratoconus. Ocular irritation, with hazing of the graft, appeared during the fourth week. ACTH was given systemically for 15 days. The eye became much less inflamed within 48 hours, and during the ensuing two weeks the graft entirely cleared. The final visual result was 6/7.5 with correction.

Keratoplasty was done on the fourth patient (prognostic group III) because of a central corneal opacity to which iris was adherent until dissected free. ACTH was given systemically over a period of 12 days during the fourth and fifth postoperative week. The ocular reaction subsided, and the graft remained clear, although epithelial edema has persisted.

The fifth patient (prognostic group IV) had previously had two unsuccessful keratoplasties in an opaque cornea, followed by edema and clouding of the graft. Opacification likewise followed this operation and the use of ACTH.

The sixth patient had had a total superficial keratectomy one year previously. His cornea was as a result, thin and considerably vascularized and offered a poor prognosis for keratoplasty (group III). At the end of the third postoperative week his eye became inflamed and the graft clouded. He was given cortisone systemically and locally during the fourth to the eighth postoperative week. The inflammatory signs disappeared during the first three days after ACTH therapy, and the graft cleared during the next two weeks. Edema of the graft later ensued, however. After receiving cortisone therapy systemically, he exhibited signs of rather severe diabetes. These gradually abated during the four months following treatment, although at the time of this report he is still taking a small amount of insulin.

The last three patients were treated with cortisone locally. The seventh patient (prognostic group II) had scars of healed severe superficial keratitis, possibly due to staphylococcic conjunctivitis. Cortisone was given locally, instillations being made every two hours for two weeks, beginning late in the fourth week. The eye promptly became white, and the graft, previously hazy, became clear over a period of two weeks.

The eighth patient (prognostic group IV) had an active corneal ulcer with an associated deep corneal infiltrate of several months' duration. He had had a similar recurrent keratitis involving the same area of his cornea for 10 years. The involved portion of the cornea was excised with a 7 mm. trephine and replaced with healthy donor corneal tissue. The eye was only moderately inflamed after operation, but haziness of the graft appeared. Local cortisone therapy was instituted, and the ocular irritation promptly subsided. The graft cleared slowly during the next three to four weeks, to give a visual result of 6/6. Therapy was continued for two months after the surgical procedure because of residual edema of the lower portion of the graft, which had practically cleared at the end of this time.

The ninth patient is still convalescing, having recently had a corneal transplantation because of a central corneal opacity due to keratoconus. His eye was considered to belong to prognostic group IV because of a previous operation, done elsewhere, which had caused an adhesion of the iris to the central scar, posterior synechia and rather pronounced corneal vascularization. His eye became irritable during the fourth week, and the graft began rapidly to haze. Cortisone therapy was started on the twenty-sixth day and caused prompt subsidence of inflammatory symptoms, with clearing of the graft in three or four days. Cortisone was then stopped temporarily, after which the inflammatory reaction and the haziness of the graft recurred. He has been under treatment with cortisone administered as drops since that time, and, although some vascularization of the cornea has occurred and some corneal haze persists, the graft is slowly clearing.

Evaluation of the effect of ACTH and cortisone in keratoplasty is extremely difficult in such a small group of cases as that just discussed. Although grafts in

eyes of prognostic group IV did poorly, the signs of ocular irritation seemed to be diminished slightly. In patients with a better prognosis, evaluation was likewise difficult, because of the uncertainty of the outcome in individual cases. However, the subsidence of inflammatory signs and the tendency of the graft to clear are somewhat encouraging.

The result was questionable.

## COMMENT

Results observed in treatment of a wide variety of lesions in 55 eyes (36 patients) with cortisone or ACTH administered systemically and in 69 eyes with cortisone administered locally in the form of drops are presented. Systemic therapy with these hormones is best suited for acute lesions, which tend to run a self-limited course, since ACTH and cortisone can be administered systemically for only a short time owing to the danger of undesirable physiological side effects. Local use of cortisone is effective only in the treatment of lesions of the anterior segment but is advantageous because the drug can be administered over a long period. In our experience, the use of cortisone in the form of drops seems innocuous, no ill effects having been observed even though in some cases the instillations were made over a period of several months.

Cortisone and ACTH seem to have identical clinical effects on ocular disease. The mechanism of action of these hormones is not yet known, but they apparently block response to various types of allergens and anaphylactic reactions as well as the effects of inflammation and some chemical irritants. The underlying allergic state is unaffected, however, and persists unchanged after withdrawal of treatment. Dramatic clearing of inflamed eyes is frequently seen shortly after the beginning of therapy in eyes which respond, but prompt recurrence takes place when treatment is stopped unless the etiological agent can be eliminated.

Cortisone and ACTH given systemically offered encouraging results in the treatment of acute focal choroiditis and endophthalmitis phacoanaphylactica (table 4). Somewhat encouraging results were obtained in the treatment of acute nongranulomatous uveitis and interstitial keratitis. More questionable benefit was obtained in the treatment of retrolental fibroplasia and optic and retrobulbar neuritis, and as postoperative therapy after keratoplasty. Evaluation of the response of these conditions in such a small series of patients is extremely difficult. For example, interstitial keratitis follows a notoriously unpredictable course, as do retrobulbar and optic neuritis. Spontaneous arrest of the disease is likewise known to occur with retrolental fibroplasia. Final conclusion must await the accumulation of further data, reported by many different observers. Suffice it to say in this paper that the results observed warrant further trial of therapy. No improvement was noticed in the treatment of chronic granulomatous uveitis, Harada's disease, angiospastic retinopathy, Tay-Sachs disease (infantile amaurotic familial idiocy) or thyrotoxic exophthalmos. Although the vitreous of eyes with chronic granulomatous uveitis occasionally showed a tendency to clear and signs of inflammation to disappear, the disease usually recurred in its original appearance shortly after cessation of therapy.

Cortisone instilled topically in the form of drops seems to offer an ideal method of treating lesions of the anterior segment which respond to cortisone or ACTH. ACTH is, of course, of no value given locally, because it exerts its physiological effect only through stimulation of the adrenal cortex. We employed a cortisone suspension made by diluting 1 cc. containing 25 mg. of the hormone to 5 cc. with

isotonic sodium chloride solution. Instillation is made at one to two hour intervals during acute phases of the condition to be treated. In chronic conditions, we have continued cortisone therapy with a maintenance dose of two instillations daily.

Encouraging results with local therapy were observed in the treatment of acute nongranulomatous anterior uveitis (iridocyclitis), endophthalmitis phacoanaphylactica, iritis due to retained lens material following attempted intracapsular extraction, syphilitic interstitial keratitis, sclerosing keratitis, superficial punctate keratitis, marginal keratitis, chronic keratoconjunctivitis due to bacterial allergy, phlyctenular keratoconjunctivitis, atypical vernal conjunctivitis (allergic) and episcleritis (table 4). We believe that, when possible, cortisone should be administered locally because of simplicity of the method, lack of irritation and absence of undesirable physiological side effects. Questionable, but slightly encouraging, results were found in the treatment of keratitis secondary to uveitis, keratitis profunda, keratitis

TABLE 4.—*Results Obtained in Treatment of Ocular Lesions with ACTH and Cortisone*

| Encouraging | Questionable | Unimproved |
|---|---|---|
| | Systemic Administration of Cortisone or ACTH | |
| Focal choroiditis | Syphilitic interstitial keratitis | Chronic diffuse granulomatous uveitis |
| Acute diffuse nongranulomatous uveitis | Optic and retrobulbar neuritis | Acute Harada's disease |
| Endophthalmitis phacoanaphylactica | Retrolental fibroplasia | Chronic Still's disease |
| | Tay-Sachs disease | Angiospastic retinopathy |
| | Keratoplasty | Thyrotoxic exophthalmos |
| | Local Instillations of Cortisone | |
| Acute anterior nongranulomatous uveitis | Syphilitic interstitial keratitis | Chronic posterior granulomatous uveitis |
| Endophthalmitis phacoanaphylactica | Keratitis metaherpetica | Acute Harada's disease |
| Retained lens material | Keratouveitis | Chronic Vogt-Koyanagi disease |
| Sclerosing keratitis | Keratoplasty | Mustard gas keratitis |
| Superficial punctate keratitis | Keratitis profunda | Chronic Stevens-Johnson disease |
| Marginal keratitis | | |
| Chronic keratoconjunctivitis (allergic) | | |
| Phlyctenular keratoconjunctivitis | | |
| Blepharoconjunctivitis (allergic) | | |
| Atypical vernal conjunctivitis | | |
| Episcleritis | | |

metaherpetica and reactions following keratoplasty. Local application was ineffective in the treatment of posterior uveitis of any type, mustard gas (2-chloroethyl sulfide) keratitis and Stevens-Johnson disease.

## SUMMARY

The physiology of ACTH and cortisone is briefly discussed.

Methods of systemic and local administration are presented, and certain precautions are outlined.

Results of the treatment of a variety of ocular lesions by systemic and local means are listed.

(*a*) Systemic therapy is of value only for acute, self-limited lesions.

(*b*) Local administration is effective only in the treatment of lesions of the anterior segment.

ACTH and cortisone are probably effective through blocking the effects of allergens and bacterial toxins.

# LOCAL USE OF CORTISONE IN OPHTHALMIC DISEASES

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CORTISONE has been used as local medication in certain ophthalmic diseases at the Massachusetts Eye and Ear Infirmary during the past six months. The purpose of this report is to record the observations and results of our experience with a series of 53 patients.

There are numerous reports in the literature of the effectiveness of intramuscular injections of pituitary adrenocorticotropic hormone (ACTH) and cortisone in treatment of diseases of the eye. There are also reports of hazards and contraindications to the systemic use of these new drugs. Thus, Thorn and associates [1] have stated:

> ACTH is contraindicated in diabetes mellitus, congestive heart failure, hypertensive cardiovascular disease, Cushing's syndrome, acne, hirsutism, osteoporosis and osteomalacia. The same limitation is true of cortisone, with the exception of hypertensive cardiovascular disease.

Other disadvantages of the systemic use of these drugs are the expense, due to the large quantity required, and the necessity of hospitalizing the patient during the course of treatment.

It was postulated that the local use of cortisone, if effective, would have five important advantages over its administration by the systemic route: (1) there is little danger of systemic reaction; (2) the cost to the patient is less; (3) hospitalization is not necessary; (4) local treatment could probably be continued almost indefinitely, and (5) a high local concentration is possible.

Accordingly cortisone was given by subconjunctival injection or topical application to a series of patients with a variety of ophthalmic diseases (uveitis, keratitis, scleritis and vernal conjunctivitis). The preparation used was cortone,[2] a microcrystalline suspension of cortisone acetate in saline solution. Subconjunctival injections were made, each cubic centimeter containing 25 mg. of cortisone acetate. A 4 per cent cocaine solution was used for local anesthesia, and the solution was injected easily through a 25 gage needle. The injections were repeated at intervals of two weeks, when indicated. For the collyrium a suspension was used, each cubic centimeter containing 5 mg. of cortisone acetate.

One series of 10 patients had a bilateral disease process in the eyes. Cortisone was injected subconjunctivally in only one eye, so that the other could be used as a control. Another series, of 10 patients, with disease in one eye only also received

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From The Howe Laboratory, Massachusetts Eye and Ear Infirmary.

1. Thorn, G. W.; Forsham, P. H.; Frawley, T. H.; Hill, S. R.; Roche, M.; Stachelin, D., and Wilson, D. L.: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:865-872, 1950.

2. Marketed by Merck & Company, Inc., Rahway, N. J.

cortisone by the subconjunctival route. A third series, of 33 patients, received cortisone as a collyrium. The patients in this series were instructed to use 1 drop

TABLE 1.—*Bilateral Conditions Treated by Subconjunctival Injection of Cortisone in One Eye Only*

| Patient | Diagnosis | No. of Injections | Each Injection, Mg. | Total Dose, Mg. | Improvement * |
|---|---|---|---|---|---|
| P. C. | Chronic iridocyclitis | 5 | 5 | 25 | ++ |
| L. M. | Chronic iridocyclitis | 1 | 5 | 5 | None |
| Th. H. | Recurrent iritis | 1 | 25 | 25 | ++++ |
| M. McG. | Sympathetic ophthalmia | 2 | 5<br>10 | 15 | None |
| E. D. G. | Sympathetic ophthalmia | 1 | 7.5 | 7.5 | None |
| A. E. | Posterior uveitis | 1 | 5 | 5 | None |
| R. A. | Chronic uveitis (sarcoid) | 2 | 12.5 | 25 | ++++ |
| A. J. | Chronic iridocyclitis | 1 | 7.5 | 7.5 | ++++ |
| J. D. | Chronic uveitis | 2 | 7.5 | 15 | None |
| A. M. | Chronic uveitis | 6 | 5 | 30 | + |

* In this table, and in tables 2 and 3, improvement occurring in 24 hours is indicated by ++++; in 48 hours, as +++; in four days, as ++, and in one week, as +.

TABLE 2.—*Results of Subconjunctival Injection of Cortisone When the Condition Was Monocular*

| Patient | Diagnosis | No. of Injections | Each Injection, Mg. | Total Dose, Mg. | Improvement * |
|---|---|---|---|---|---|
| S. A. | Chorioretinitis | 1 | 25 | 25 | ++ |
| E. M. | Rodent ulcer of cornea | 1 | 5 | 5 | None |
| B. K. | Sclerokeratitis | 7 | 5 | 35 | ++++ |
| O. B. | Chorioretinitis | 5 | 5 to 12.5 | 42 | None |
| J. C. | Eales's disease | 2 | 5 | 10 | None |
| H. McC. | Chronic sclerokeratitis | 2 | 5<br>7.5 | 12.5 | None |
| W. H. | Marginal corneal ulcer | 1 | 7.5 | 7.5 | + |
| R. C. | Acute sclerokeratitis | 1 | 7.5 | 7.5 | +++ |
| M. S. | Chronic sclerokeratitis | 2 | 5 | 10 | ++ |
| N. C. | Acute iritis | 1 | 5 | 5 | ++++ |

TABLE 3.—*Cortisone Used as a Collyrium*

| Patient | Diagnosis | Improvement | Patient | Diagnosis | Improvement |
|---|---|---|---|---|---|
| N. C. | Acute iritis | +++ | W. M. | Disciform keratitis | + |
| M. C. | Acute iritis | ++++ | M. S. | Bullous keratitis | ++ |
| M. H. | Acute iritis | + | P. C. | Bullous keratitis | ++ |
| K. P. | Acute iritis | ++++ | R. G. | Relapsing keratitis | +++ |
| R. D. | Acute iritis | None | M. T. | Relapsing keratitis | +++ |
| M. E. | Acute iritis | None | M. C. | S. punctate keratitis * | + |
| V. D. | Acute iritis | ++++ | M. B. | S. punctate keratitis | +++ |
| J. F. | Chronic uveitis | +++ | B. M. | S. punctate keratitis | ++++ |
| P. C. | Chronic uveitis | None | R. A. | S. punctate keratitis | +++ |
| M. B. | Chronic uveitis | ++ | W. D. | Acute sclerokeratitis | ++++ |
| M. F. | Chronic uveitis | ++ | B. H. | Acute sclerokeratitis | ++++ |
| M. J. | Chronic uveitis (sarcoid) | ++++ | H. M. | Chronic sclerokeratitis | ++++ |
| O. B. | Chorioretinitis | None | M. S. | Chronic sclerokeratitis | ++++ |
| M. M. | Postoperative uveitis | +++ | W. H. | Marginal ulcerative keratitis | ++++ |
| R. C. | Sympathetic ophthalmia | ++ | K. M. | Discharging socket | + |
| E. D. G. | Sympathetic ophthalmia | +++ | F. P. | Vernal conjunctivitis and keratitis | +++ |
| M. McG. | Sympathetic ophthalmia | + | | | |

* Superficial punctate keratitis.

every hour while awake, and as improvement occurred the frequency was gradually decreased.

The data regarding these patients are summarized in tables 1 to 3.

## COMMENT

Little or no pain occurs with subconjunctival injections of 7.5 mg. or less, but there is often considerable discomfort when 12.5 mg. or more is injected. A crystalloid substance, presumably cortisone, can be seen subconjunctivally for one to two weeks after injection; so complete absorption must take at least two weeks.

In a number of instances it has been necessary to continue the use of the collyrium for long periods to prevent recurrence of the disease process. One patient has used the collyrium in both eyes for 14 weeks, with benefit and no ill effects.

The favorable response to the collyrium of such stubborn conditions as superficial punctate keratitis, sclerokeratitis, relapsing keratitis and bullous keratitis is definite. The collyrium was particularly effective in relieving promptly the pain, photophobia and itching often associated with these diseases.

It is interesting that such diverse conditions as sclerokeratitis and relapsing keratitis respond to cortisone. It is also interesting that some diseases which are similar clinically varied greatly in their response to cortisone. Thus, four patients with acute uveitis showed prompt response to the collyrium, and two others showed no improvement. Three patients with sclerokeratitis responded well to subjunctival injections, and a fourth (H. M.) was not improved, although she responded promptly to the use of collyrium.

Two patients who had become sensitive to atropine and scopolamine were able to continue the use of these drugs without difficulty when cortisone as a collyrium was also administered.

The local use of cortisone was not definitely beneficial in treatment of rodent ulcer of the cornea or in Eales's disease or in three of 12 patients with uveitis. One patient with severe chorioretinitis showed no benefit from rather intensive local treatment with cortisone.

## CONCLUSIONS

As cortisone was used in this series of 53 patients, it was more effective when administered as a collyrium than as subconjunctival injections.

The local use of cortisone was more effective in diseases of the anterior segment than in those of the posterior segment of the globe.

The collyrium was definitely effective in treatment of sclerokeratitis, superficial punctate keratitis, bullous keratitis and relapsing keratitis.

The local use of cortisone was not definitely effective in treatment of Eales's disease or rodent ulcer of the cornea or in one fourth of the patients with uveitis. One patient with severe chorioretinitis showed no benefit from the intensive local use of cortisone.

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# EARLY CLINICAL RESULTS OF ACTH AND CORTISONE TREATMENT OF OCULAR DISEASES

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THE CLINICAL material incorporated in this paper is the product of a cooperative effort by representatives of the largest eye clinics in the Chicago metropolitan area who, at the instigation of the Chicago Ophthalmological Society, agreed to pool their initial experiences with the use of pituitary adrenocorticotropic hormone (ACTH) and cortisone (11-dehydro-17-hydroxycorticosterone) in ophthalmic diseases in order to obtain a more comprehensive understanding of the use, indications and therapeutic spectrum of these agents. The information here contained is presented primarily from the point of view of practical clinical ophthalmology, without reference to favorable or unfavorable effects on associated systemic diseases or to any unfavorable physical or mental alterations for which the therapeutic agent might be held responsible. Each clinic reported its total experiences with these drugs. Consequently, although the bulk of the cases belong in those categories where the available literature indicates one might expect fruitful results, there are in addition a fair number of cases reported in which the use of these drugs might be indicated from the nature of the pathological process present or in which their use was empirical (referable to the local use of cortisone only).

As one might expect, the daily and total doses of these drugs varied considerably among institutions. In general, however, the daily dose of ACTH ranged from 40 to 75 mg. daily, and the therapy was continued for from seven to 10 days.

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This paper is the report of a symposium held at the meeting of the Chicago Ophthalmological Society, Oct. 2, 1950; J. Robert Fitzgerald, M.D., moderator. The following clinics were represented: Passavant Memorial Hospital and Cook County Hospital (Dr. Bellows); Presbyterian Hospital (Dr. Donegan); St. Luke's Hospital (Dr. Gamble); Albert Merritt Billings Hospital (Dr. Krause); Wesley Memorial Hospital and Veterans Administration Hospital (Dr. Mann); Illinois Eye and Ear Infirmary and Research and Educational Hospitals, University of Illinois (Dr. Pearlman), and Michael Reese Hospital (Dr. Zekman).

Usually the daily dose was divided into four injections. Cortisone, on the other hand, was most frequently given in single daily injections of 100 mg. for an average of 10 days. In most instances cortisone (25 mg.) was used locally in isotonic

TABLE 1.—*Acute Nongranulomatous Uveitis*

A. Systemic Treatment

| Drug | Dose (Mg.) Daily | Dose (Mg.) Total | Results Improved | Results Not Improved | Improvement, Days | Recovery, Days | Recurrence or Relapse | Time of Observation, Mo. | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Cortisone | 100 | 1,000 | 1 | .. | 4 | 14 | None | 1 | Postoperative uveitis |
| ACTH | 75 | 250 | 1 | .. | 4 | 10 | None | 7 | ..... |
| ACTH | 75 | 337 | 1 | .. | 3 | 5 | None | 6½ | ..... |
| ACTH | 60 | 240 | 1 | .. | 2 | 10 | None | 6½ | ..... |
| ACTH | 60 to 100 | 6,930 | .. | 1 | .. | .. | Continued activity | 8 | Associated with severe rheumatoid arthritis and psoriasis |
| Cortisone | 100 | 2,000 | 1 | .. | 4 | 12 | None | 4 | Immediate relief of pain |
| Cortisone | 100 | 700 | 1 | .. | 5 | 9 | None | 4 | Pain and photophobia, bilateral relief in 4 hr. |
| ACTH | ? | ? | 1 | .. | 10 | 20 | None | 6 | Bilateral uveitis |
| Cortisone | 100 | 400 | 1 | .. | 4 | 4 | None | 6 | ..... |
| Cortisone | 100 | 1,000 | 1 | .. | 5 | 10 | None | 6 | Traumatic origin; "cortisone saved eye from enucleation" |
| ACTH | 75 | Estimate 600 | 1 | .. | .. | 6 | ? | .. | ..... |
| ACTH | 50 | Estimate 500 | 1 | .. | 1 | 6 | ? | .. | ..... |
| ACTH | 50 | Estimate 500 | .. | 1 | .. | .. | .. | .. | ..... |

Summary

| | | | |
|---|---|---|---|
| No. of patients | 13 | Improvement noted in | 4.2 days (average) |
| No. improved | 11 | Recovery noted in | 10 days (average) |
| No. not improved | 2 | Relapses or recurrences | None noted |
| | | Average time of observation | 5 mo. |

B. Local Treatment with Cortisone

| Dilution | Frequency | Results Improved | Results Not Improved | Improvement, Days | Recovery, Days | Recurrence or Relapse | Time Observed | Comment |
|---|---|---|---|---|---|---|---|---|
| 1:4 (ointment) | ..... | 1 | .. | 2 | 2 | None | 1 mo. | ..... |
| 1:4 | q. h. | 1 | .. | 2 | 10 | None | 3½ mo. | ..... |
| 1:4 | q. h. | 1 | .. | 1 | 8 | 10 days after treatment stopped | 4 mo. | Recurrence promptly controlled when treatment was resumed |
| 1:4 | q. h. | 1 | .. | 4 | 10 | None | ..... | ..... |
| 1:4 | q. h. | 1 | .. | 4 | 8 | None | ..... | ..... |
| 1:4 | q. 2 h. | 1 | .. | 2 | 4 | None | ..... | ..... |
| 1:4 | q. 2 h. | 1 | .. | 2 | 5 | None | ..... | ..... |
| 1:1 | q. h. | 1 | .. | ? | 10 | None | 1 mo. | Also had one course typhoid therapy |
| 1:1 | q. h. | 1 | .. | ? | 7 | None | 25 days | ..... |
| 1:1 | q. h. | 1 | .. | ? | 18 | None | 25 days | ..... |
| 1:1 | q. h. | 1 | .. | ? | 6 | None | 7 days | ..... |
| 1:1 | q. h. | 1 | .. | ? | 4 | ? | 8 days | ..... |
| 1:1 | q. h. | .. | 1 | .. | .. | ..... | ..... | ..... |

Summary

| | | | |
|---|---|---|---|
| No. of patients | 13 | Improvement noted in | 2.7 days (average) |
| No. improved | 12 | Recovery noted in | 8 days (average) |
| No. not improved | 1 | Relapse or recurrence | 1 case |
| | | Average time observed | 2 mo. |

sodium chloride solution diluted 1:4, 1 drop being instilled every one to two hours. In some instances the full strength cortisone solution was instilled (1 cc. contains 25 mg.). In others liquid petrolatum U.S.P., 1 per cent methyl cellulose or an ointment base was used as a vehicle.

A total of 198 patients with ocular diseases treated with these agents are reported, of whom 106 had uveitis, either anterior or posterior; 14 had primary pathological lesions in the retina or the optic nerve; 29 had external ocular disorders; 27, primary corneal disease, and 22, miscellaneous ocular conditions. For purposes of clarification, the reports on uveitis are divided primarily into anterior and posterior uveitis. All cases of anterior uveitis are further subdivided into those of the acute and those of the chronic granulomatous and nongranulomatous forms, with the exception of five case of sympathetic ophthalmia,

TABLE 2.—*Acute Granulomatous Uveitis Treated Systemically with ACTH or Cortisone*

| Drug | Dose (Mg.) Daily | Dose (Mg.) Total | Results Improved | Results Not Improved | Improvement, Days | Recovery, Days | Recurrence or Relapse | Time Observed, Mo. | Comment |
|---|---|---|---|---|---|---|---|---|---|
| ACTH | 40 | 280 | 1 | .. | 2 | 5 | None | 1 | "Cyclitic crisis" |
| ACTH | 20 to 50 | 530 | 1 | .. | 3 | 14 | None | 2 | Bilateral involvement; gland biopsy showed histological evidence of "Hodgkin's disease" |
| ACTH | 50 | 550 | 1 | .. | .. | 11 | None | 1 | Onset 2 mo. after successful lens extraction in opposite eye |
| Cortisone<br>ACTH | 100<br>40 | 300<br>1,030 | .. | 1 | .. | .. | Continued activity | 6 | Associated with severe rheumatoid arthritis and ulcerative colitis |
| Cortisone | 100 | 2,000 | 1 | .. | 5 | 21 | None | 6 | More rapid recovery with cortisone than with any other treatment in previous episodes |
| Cortisone | 100 | 1,000 | 1 | .. | 5 | 14 | None | 4 | 4+ Wassermann reaction; no antisyphilitic treatment |
| Cortisone and cortisone locally | 100 | 1,000 | 1 | .. | 3 | 10 | None | 3 | ..... |
| ACTH | 80 | 330 | 1 | .. | 2 | 7 | None | 8 | Episcleritis, which cleared simultaneously |
| ACTH | 50 | 350 | 1 | .. | 2 | 4 | ? | Hospital observation only | Allergic etiology probable |
| ACTH<br>Cortisone | 40<br>1:1 | 590<br>q. 2 hr. | 1 | .. | ? | 10 | ..... | 1 | ..... |

Summary

| | | | |
|---|---|---|---|
| No. of patients | 10 | Improvement noted in | 3 days (average) |
| No. improved | 9 | Recovery noted in | 11 days (average) |
| No. not improved | 1 | Average time observed | 3 mo. + |
| | | No. of relapses or recurrences | None |

which are reported separately. When pertinent, the therapeutic effect of parenteral treatment with either ACTH or cortisone is contrasted with that of the local use of cortisone. Since in the final analysis the effectiveness of any therapeutic measure is judged by the rapidity and the permanence with which it arrests a pathological process and permits nature to return the tissue to its normal physiological state, in cases showing "clinical improvement" data are furnished on the number of days of treatment required, first, to improve the clinical situation and, second, to restore the diseased organ to its presumed preinflammatory state. In addition, information is furnished on the incidence of relapses or recurrences. Data concerning recurrence are perhaps not very valid, as the period of observation in many instances was far too brief to be clinically significant. Clinical improvement was judged by the following criteria: subsidence of subjective manifestations of the

TABLE 3.—*Chronic Nongranulomatous Uveitis*

A. Systemic Treatment

| Drug | Dose (Mg.) Daily | Dose (Mg.) Total | Results: Improved | Results: Not Improved | Improvement, Days | Recovery, Days | Recurrence or Relapse | Time Observed | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Cortisone | 100 | 1,100 | .. | 1 | .. | .. | .. | 3 mo. | Lentigenic with secondary glaucoma |
| Cortisone | 100 | 1,450 | .. | 1 | .. | .. | .. | 3 mo. | Lentigenic |
| Cortisone | 100 | 800 | .. | 1 | .. | .. | .. | 1 mo. | Lentigenic with secondary glaucoma |
| ACTH | 80 | 480 | .. | 1 | .. | .. | .. | 1 mo. | Associated with syphilitic interstitial keratitis |
| ACTH | 50 | 550 | .. | .. | .. | .. | .. | ..... | Postoperative with secondary glaucoma; eye later enucleated |
| Cortisone locally | 1:1 | ... | .. | 1 | .. | .. | .. | ..... | ..... |
| ACTH | 40 | 440 | .. | .. | .. | .. | .. | ..... | ..... |
| Cortisone | 1:1 | q. h. | 1 | .. | 21 | ? | .. | 30 days | Marie-Strümpell disease |
| ACTH | 40 | 1,910 | 1 | .. | ? | ? | .. | ..... | Bilateral cataracta complicata; cataract removed (R. E.) with subsequent phthisis; cataract removed (L. E.) under and after ACTH therapy, with smooth postoperative course; vitreous still hazy from original inflammatory process |
| Cortisone | 1:1 | q. h. | .. | 1 | .. | .. | .. | ..... | ..... |

Summary
No. of patients..... 8
No. improved..... 2
No. not improved..... 6

B. Local Treatment with Cortisone

| Dilution | Frequency | Results: Improved | Results: Not Improved | Improvement, Days | Recovery, Days | Recurrence or Relapse | Time Observed | Comment |
|---|---|---|---|---|---|---|---|---|
| 1:4 (ointment) | ..... | 1 | .. | 10 | .. | None | 1 mo. | Associated with transient glaucoma |
| 1:4 (ointment) | ..... | .. | 1 | .. | .. | ..... | 1 mo. | Associated with glaucoma |
| 1:4 (ointment) | ..... | .. | 1 | .. | .. | ..... | 2 mo. | ..... |
| 1:4 (ointment) | ..... | 1 | .. | 7 | 35 | None | 2 mo. | ..... |
| 1:4 (Methyl cellulose) | ..... | 1 | .. | 7 | 21 | None | 2 mo. | ..... |
| 1:4 (Methyl cellulose) | ..... | .. | 1 | .. | .. | ..... | 1 mo. | Lentigenic |
| 1:4 (Liquid petrolatum U. S. P.) | ..... | 1 | .. | 7 | 28 | None | 2 mo. | ..... |
| 1:4 (Liquid petrolatum U. S. P.) | ..... | 1 | .. | 7 | 14 | None | 1 mo. | ..... |
| 1:4 | q. i. d. | 1 | .. | 2 | 2 | None | ..... | ..... |
| 1:4 | q. i. d. | 1 | .. | 4 | 7 | None | ..... | ..... |
| 1:4 | q. 2 h. | 1 | .. | 4 | 7 | None | ..... | ..... |
| 1:4 | q. 2 h. | 1 | .. | 2 | 5 | None | ..... | ..... |
| 1:4 | q. 2 h. | 1 | .. | 4 | 7 | None | ..... | ..... |
| 1:4 | q. 2 h. | 1 | .. | 3 | 5 | Yes | 2 mo. later | ..... |
| 1:4 | q. 2 h. | .. | 1 | .. | .. | ..... | ..... | Causative tuberculosis also treated with streptomycin and paraaminosalicylic acid |

Summary
No. of patients..... 15
No. improved..... 11
No. not improved..... 4

Improvement noted in..... 5 days (average)
Recovery in..... 13 days (average)
Recurrence in 1 case..... 2 mo. later

TABLE 4.—*Chronic Granulomatous Uveitis*

A. Systemic Treatment

| Drug | Dose, Mg. Daily | Dose, Mg. Total | Results Improved | Results Not Improved | Improvement, Days | Recovery, Days | Recurrence or Relapse | Time Observed, Mo. | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Cortisone | 100 | 1,700 | .. | 1 | .. | .. | ..... | 1 | Remarkable recovery with tuberculin after treatment with cortisone |
| Cortisone | 100 | 1,100 | 1 | .. | 4 | 4 | None | 6 | Cortisone given before and after lens extraction; uneventful postoperative course; postoperative vision 20/20 |
| Cortisone | 100 | 1,400 | 1 | .. | 5 | 14 | None | 6 | Bilateral; 10 mo. duration; all other treatment unavailing |
| Cortisone | 100 | 1,400 | .. | 1 | .. | .. | ..... | .. | Associated with bullous keratitis and secondary glaucoma |
| ACTH | 100 | 1,445 | 1 | .. | 4 | 19 | None | 6 | ..... |
| ACTH | 100 | 1,040 | 1 | .. | 8 | 14 | None | 6½ | ..... |

Summary

| | | | |
|---|---|---|---|
| No. of cases | 6 | Improvement noted in | 5 days (average) |
| No. improved | 4 | Recovery noted in | 13 days (average) |
| No. not improved | 2 | Recurrence or relapse | None |

B. Local Treatment with Cortisone

| Dilution | Frequency | Results Improved | Results Not Improved | Improvement, Days | Recovery, Days | Recurrence or Relapse | Time Observed, Mo. | Comment |
|---|---|---|---|---|---|---|---|---|
| 1:4 (ointment) | ..... | 1 | .. | 7 | 21 | None | 2 | ..... |
| 1:4 (ointment) | ..... | 1 | .. | 7 | 14 | None | 1 | ..... |
| 1:4 (ointment) | ..... | .. | 1 | .. | .. | ..... | 2 | ..... |
| 1:4 (ointment) | ..... | .. | 1 | .. | .. | ..... | 1 | ..... |
| 1:4 (methyl cellulose) | ..... | 1 | .. | 7 | 21 | None | 2 | ..... |
| 1:4 (methyl cellulose) | ..... | .. | 1 | .. | .. | ..... | 1 | ..... |
| 1:4 (liquid petrolatum U. S. P.) | ..... | .. | 1 | .. | .. | ..... | 1 | ..... |
| 1:4 | q. h. | 1 | .. | 12 | .. | ..... | 7 | Inflammation subsided in 12 days; keratic precipitates, synechias, etc., persist |

Summary

| | |
|---|---|
| No. of patients | 8 |
| No. improved | 4 |
| No. not improved | 4 |

TABLE 5.—*Sympathetic Ophthalmia*

| Clinical History | Treatment | Histological Proof | Results | Relapse After Withdrawal of Treatment |
|---|---|---|---|---|
| L. E.: Iridencleisis 4 mo. earlier, eye remaining irritable<br>R. E.: Inflammatory activity of 1 wk. duration | (1) ACTH, 75 mg. daily<br>(2) Enucleation of L. E. | + | Improvement in R. E. in 3 days; disappearance of cells and keratic precipitates in 9 days | None |
| L. E.: Cataract extraction 3 mo. previously<br>R. E.: Inflammatory activity 1 mo. | (1) Fever and antibiotic therapy unavailing<br>(2) ACTH, 50 mg. daily | — | Improvement in 48 hr.; complete absence of cells and keratic precipitates in 8 days | None |
| Perforating injury followed by sympathetic inflammation in opposite eye | (1) Cortisone, 100 mg. daily; total dose, 2,100 mg.<br>(2) Enucleation of traumatized eye | + | No improvement | ..... |
| ? | ACTH, 50 mg. daily; total dose, 550 mg. | + | Improvement in 3 days; eye quiescent in 8 days; subsequent relapse with loss of vision to light perception | Yes |
| Onset 6 wk. after cataract extraction | Cortisone, 100 mg. daily; total dose, 1,100 mg. | — | No improvement | ..... |

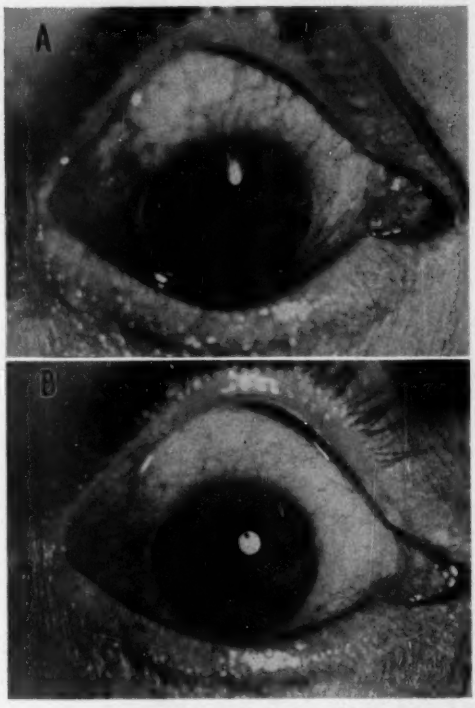


Fig. 1 (P. P.).—*A*, granulomatous iritis of three months' duration. No improvement had resulted from the use of antibiotics, fever therapy or other previous treatment. *B*, two weeks after institution of ACTH therapy, 100 mg. daily.

Fig. 2 (P. P.).—Eighteen days after beginning of ACTH therapy. The eye was white, with only a few keratic precipitates. No cells or aqueous flare was apparent. The pupil was evenly dilated.

TABLE 6.—*Choroiditis and Posterior Uveitis*

A. Acute Form

| Diagnosis | Drug | Dose, Mg. | | Results | | Time to Improvement, Days | Recovery, Days | Recurrence or Relapse | Time Observed, Mo. | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Daily | Total | Improved | Not Improved | | | | | |
| Acute choroiditis | Cortisone | 100 | 900 | 1 | .. | 21 | 42 | None | 3 | ..... |
| Acute choroiditis | Cortisone | 100 | 900 | 1 | .. | 14 | .. | None | 2 | ..... |
| Acute chorioretinitis | ACTH | 100 | 850 | 1 | .. | 6 | 12 | None | 4 | Vision normal in 12 days |
| Acute chorioretinitis | ACTH | 100 | 1,250 | 1 | .. | 8 | 10 | None | 3 | Vision normal in 10 days |
| Acute chorioretinitis | ACTH | 100 | 800 | 1 | .. | 4 | 12 | None | 5 | Vision normal in 12 days |
| | Cortisone | 100 | 700 | .. | .. | .. | .. | ..... | .. | ..... |
| Acute chorioretinitis | ACTH | 100 | 350 | 1 | .. | 5 | 10 | None | 2 | Vision normal in 10 days |
| | Cortisone | 100 | 400 | .. | .. | .. | .. | ..... | .. | ..... |
| Acute chorioretinitis with retinal detachment and tear | ACTH | 100 | 2,050 | 1 | .. | 12 | 22 | None | 3 | Temporal retina elevated 12 D.; tear sealed and retina flat after 22 days of treatment |
| Acute central choroiditis | Cortisone | 100 | 2,000 | 1 | .. | 4 | 12 | Yes | 9 | Associated with subacute bacterial endocarditis; 3 recurrences; all cleared with cortisone; final vision 20/25 |
| Acute choroiditis; high myopia; Fuchs's spot in macula | Cortisone | 100 | 1,000 | .. | 1 | .. | .. | ..... | 6 | ..... |
| Acute central choroiditis | Cortisone | 100 | 4,000 | 1 | .. | 7 | 14 | Three | 6 | Each recurrence controlled with cortisone; final vision 20/30 |
| Acute central choroiditis | Cortisone | 100 | 1,000 | 1 | .. | 4 hr. | 6 | None | 2 | Visual acuity 20/200; vision 20/70 4 hr. after treatment; 20/40 24 hr. after therapy and 20/25 6 days after treatment |
| Acute central choroiditis | Cortisone | 100 | 1,000 | 1 | .. | 3 | 14 | None | 3 | Vitreous exudate cleared in 3 days |
| Acute central choroiditis | Cortisone | 100 | 1,000 | 1 | .. | 3 | 10 | None | 3 | ..... |
| Acute central choroiditis | ACTH | ? | ? | 1 | .. | 4 | 7 | None | 6 | Duration 4 mo. prior to treatment; recovery with visual acuity 20/40 |
| Acute juxtapapillary choroiditis | Cortisone | 100 | 1,200 | 1 | .. | 7 | 21 | None | 6 | ..... |
| Acute chorioretinitis | ACTH | 50-75 | 1,000 | 1 | .. | 10 | 16 | Yes | 1 | Also given typhoid H |
| Acute choroiditis | ACTH | 40 | 280 | .. | 1 | .. | .. | ..... | 1 | Tuberculin reaction |

Summary

No. of cases..... 17
No. improved..... 15
No. not improved..... 2

Improvement noted in..... 7 days (average)
Recovery noted in..... 15 days (average)

B. Chronic Form

| Diagnosis | Drug | Dose, Mg. | | Results | | Improvement, Days | Recovery, Days | Recurrence or Relapse | Time Observed, Mo. | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Daily | Total | Improved | Not Improved | | | | | |
| Chronic choroiditis | Cortisone | 100 | 1,200 | .. | 1 | .. | .. | ..... | 1 | ..... |
| Chronic choroiditis | Cortisone | 100 | 900 | 1 | .. | 14 | 28 | None | 3 | ..... |
| Chronic chorioretinitis; high myopia | ACTH | 100 | 1,225 | .. | 1 | .. | .. | ..... | 5½ | ..... |
| Central chorioretinitis, old healed | ACTH | 100 | 1,062 | .. | 1 | .. | .. | ..... | 6 | ..... |
| Chronic chorioretinitis; optic neuritis | ACTH | 100 to 150 | 1,400 | .. | 1 | .. | .. | ..... | 3 | Some clearing of vitreous |
| Chronic chorioretinitis | ACTH | 100 | 910 | .. | 1 | .. | .. | ..... | 6½ | Some clearing of vitreous |
| Chronic central choroiditis, bilateral | Cortisone | 100 | 1,000 | .. | 1 | .. | .. | ..... | 6 | Probably due to flash injury |
| Chronic central choroiditis, bilateral | Cortisone | 100 | 1,000 | 1 | .. | 5 | Incomplete recovery | ..... | 6 | Subjective improvement |
| Chronic disseminated choroiditis, bilateral | Cortisone | 100 | 2,000 | 1 | .. | 7 | 14 | Yes | 5 | Clearing of vitreous exudate |
| Chronic choroiditis; bilateral myopia | Cortisone | 100 | 3,000 | 1 | .. | 5 | Incomplete recovery | Yes | 6 | Marked subjective visual improvement |
| Chronic disseminated choroiditis | Cortisone | 100 | 5,000 | 1 | .. | 7 | Incomplete recovery | Yes | 6 | Associated with diabetes and hypertension |

Summary

No. of cases..... 11
No. improved..... 5 (3 incomplete recovery)
No. not improved..... 6

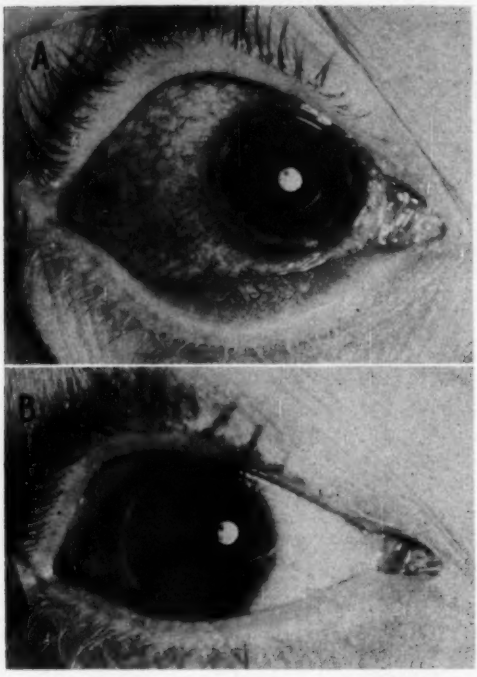


Fig. 3 (R. S.).—*A*, acute nongranulomatous iritis of three weeks' duration. No improvement had been noted under the usual therapy. *B*, nine days after institution of ACTH, 100 mg. daily.

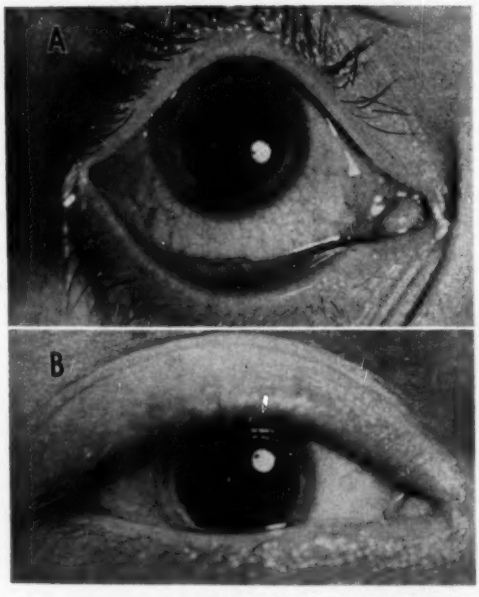


Fig. 4 (L. R.).—*A*, acute nongranulomatous iritis of four weeks' duration, resistant to treatment with atropine, heat and fever (typhoid) therapy. *B*, five days after beginning of local cortisone therapy.

disease; clearing of the media; resolution of ocular hyperemia and by-products of the inflammation, and unequivocal visual improvement when organically or clinically possible.

A total of 26 patients with acute nongranulomatous uveitis are reported, 13 of whom were treated systemically (table 1 A) and 13 locally (table 1 B). Of the

TABLE 7.—*Retina and Optic Nerve*

| Diagnosis | No. of Cases | Drug | Dilution | Dose, Mg. | | Results | | Comment |
|---|---|---|---|---|---|---|---|---|
| | | | | Daily | Total | Improved | Not Improved | |
| Senile macular degeneration... | 1 | ACTH | ... | 50 | 250 | .. | 1 | ..... |
| Senile macular degeneration... | 4 | Cortisone | 1:4 | .. | ... | .. | 4 | ..... |
| Disciform macular degeneration ..... | 1 | ACTH | ... | 60 | 600 | .. | 1 | ..... |
| Kuhnt-Junius disease..... | 1 | Cortisone | ... | 100 | 1,000 | .. | 1 | ..... |
| Central vein thrombosis with absolute glaucoma..... | 2 | Cortisone | 1:4 | .. | ... | .. | 2 | Relief of pain in both cases but no change in basic ocular condition |
| Angiospastic retinopathy..... | 1 | Cortisone | ... | 100 | 1,100 | 1 | .. | Improvement in 6 days; no recurrence in 6 mo. |
| Angiospastic retinopathy..... | 1 | Cortisone | ... | 100 | 1,000 | 1 | .. | Improvement in 4 days; recovery in 7 days |
| Angiospastic retinopathy..... | 1 | Cortisone | ... | 100 | 1,000 | 1 | .. | Improvement in 5 days; recovery in 14 days |
| Optic neuritis..... | 1 | ACTH | ... | 50 | 250 | .. | 1 | ..... |
| Retrobulbar neuritis..... | 1 | ACTH | ... | 50 | 250 | .. | 1 | ..... |

TABLE 8.—*External Ocular Diseases*

| Diagnosis | No. of Cases | Drug | Dilution | Dose, Mg. | | Results | | Comment |
|---|---|---|---|---|---|---|---|---|
| | | | | Daily | Total | Improved | Not Improved | |
| Episcleritis ..... | 2 | ACTH | ... | 50 | 250 | 2 | .. | All eyes showed rapid and complete healing in 2 to 4 days |
| Episcleritis ..... | 8 | Cortisone, locally | 1:4 | .. | ... | 8 | .. | |
| Sclerokeratitis ..... | 7 | Cortisone, locally | 1:4 | .. | ... | 7 | .. | Marked tendency to recurrence even after 2-3 mo. of treatment |
| Phlyctenular keratitis..... | 4 | Cortisone, locally | 1:4 | .. | ... | 4 | .. | Recovery rapid and complete |
| Ocular pemphigus..... | 1 | Cortisone, locally | 1:4 | .. | ... | .. | .. | No response to local use of cortisone; prompt disappearance of symptoms with ACTH |
| | | ACTH | ... | 100 | 1,000 | 1 | .. | |
| Allergic conjunctivitis..... | 1 | Cortisone, locally | 1:4 | .. | ... | 1 | .. | Failure of all other treatment for 18 mo.; complete relief of symptoms in 24 hr.; effect persistent |
| Acute conjunctivitis, nonspecific | 5 | Cortisone, locally | 1:4 | .. | ... | 5 | .. | Failure after 2 mo. of usual treatment; prompt healing with cortisone |
| Conjunctivitis associated with Guyton implant | 1 | Cortisone, locally | 1:4 | .. | ... | . | 1 | ..... |

patients treated systemically with either ACTH or cortisone, 11 showed improvement and two no improvement. With local cortisone therapy (table 1 B) 12 were improved and one was not improved. The average number of days of treatment before improvement was noted was four days for systemic management and three days for local therapy. Complete recovery was noted in an average of 10 days in the systemically treated patients and in eight days in the group with local

therapy. Ten patients with acute granulomatous uveitis are reported (table 2), all of whom were treated systemically, with improvement in nine. The rapidity of improvement was comparable to that in the group with acute nongranulomatous uveitis. Comparison of the two drugs used systemically indicated similar therapeutic efficiency. Of the 8 patients with chronic nongranulomatous uveitis (table 3 A), only two showed improvement, and these received combined systemic and local treatment. However, in three of the six patients who did "not improve," the disease was lentigenic, and another had a positive serologic reaction for syphilis and interstitial keratitis. Fifteen patients with chronic nongranulomatous uveitis (table 3 B) had local therapy, 11 of whom were classified as "improved" in an average of five days and as "recovered" in an average of 13 days. Of 14 patients with chronic granulomatous uveitis, six were treated systemically (table 4 A). Of these, four were "improved" in an average of five days and made a clinical recovery in an average of 13 days after the start of treatment. Of the eight patients treated locally (table 4 B), the condition of four was improved. Relapses and recurrences were infrequent, and when they did occur they tended to respond to similar therapy in the same manner as the initial process. Information concerning the response to systemic therapy following failure of local treatment was insufficient to indicate any clinical trend. This point must await further clinical evaluation. Of the five patients with clinical or pathologically proved sympathetic ophthalmia (table 5), three were treated with ACTH, two of whom made a rather spectacular recovery. A third patient showed initial improvement but subsequently relapsed, with loss of vision to light perception. The other two patients were treated with cortisone, without benefit. A total of 28 patients with posterior uveitis (choroiditis and chorioretinitis) were treated; 17 of these had the acute and 11 the chronic form. Of the 17 patients with the acute form (table 6 A), 15 showed "improvement" in an average of seven days and made a clinical "recovery" in an average of 15 days. Of the 11 patients with the chronic disease (table 6 B), only five were "improved," and of these only two made clinical recoveries. Relapses and recurrences were again infrequent.

In 14 patients the primary pathologic lesion was in the retina or the optic nerve (table 7). No significant results were obtained, with the possible exception of three patients with angiospastic retinopathy, in whom, in the opinion of the supervising ophthalmologist, the results were as good as, if not somewhat better than, the anticipated clinical improvement with any other form of treatment.

Of the 29 patients with external ocular diseases (table 8), most of whom were treated with cortisone locally, rapid recovery was almost universally noted, and this improvement was sustained in all cases except those of sclerokeratitis, in which a strong tendency to relapse was noted even after two to three months of therapy.

A variety of corneal conditions (table 9) were treated, chiefly with local instillations of cortisone. None was represented by a sufficient number of cases to have any clinical significance, except for rosacea keratitis (3 cases) and dendritic ulcer (4 cases), in all of which recovery was rather spectacular, without relapse.

Of chief interest in the miscellaneous group of ocular conditions reported (table 10) was the absence of favorable results in six cases of retrolental fibroplasia. However, in the secondary form of glaucoma due to this condition, as well as in secondary glaucoma from other causes, several of the authors reported favorably

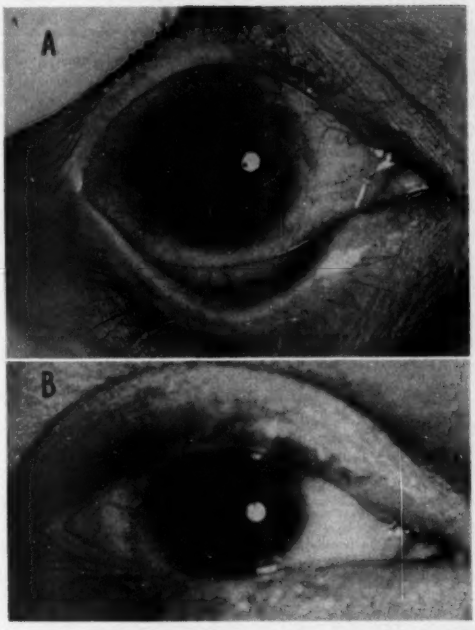


Fig. 5 (V. B.).—*A*, sclerosing keratitis present for two years with remissions and exacerbations. Present attack was of four weeks' duration, with no improvement from fever (typhoid) therapy, antibiotics or desensitization to tuberculin. *B*, 18 days after beginning of local cortisone therapy.

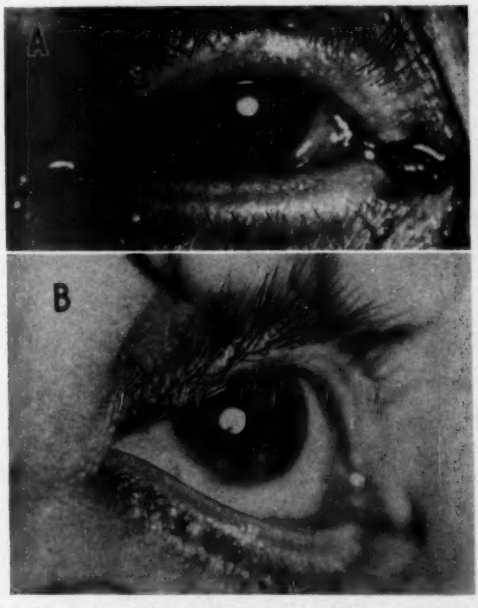


Fig. 6 (M. T.).—*A*, phlyctenular keratoconjunctivitis with intense photophobia and injection. *B*, one week after institution of local cortisone therapy.

TABLE 9.—*Corneal Diseases*

| Diagnosis | No. of Cases | Drug | Dilution | Dose, Mg. | | Results | | Comment |
|---|---|---|---|---|---|---|---|---|
| | | | | Daily | Total | Improved | Not Improved | |
| Rosacea keratitis | 1 | ACTH | ... | 50 | 250 | 1 | .. | Improved 2 days; healed 4 days |
| Rosacea keratitis | 1 | Cortisone, locally | 1:4 | .. | ... | 1 | .. | Rapid recovery |
| Dendritic ulcer | 1 | Cortisone, locally | 1:1 | .. | ... | 1 | .. | Disease had failed to respond to other treatment |
| Dendritic ulcer | 3 | Cortisone, locally | 1:4 | .. | ... | 3 | .. | Prompt healing in all cases |
| Severe undiagnosed keratitis | 1 | ACTH | ... | 40 | 280 | .. | .. | Resisted all treatment for 9 mo.; complete recovery in few days |
| | | Cortisone, locally | 1:1 | .. | ... | 1 | .. | |
| Keratitis sicca (arthritis) | 1 | ACTH | ... | 40-60 | 1,000 | .. | 1 | Symptoms relieved by artificial tears |
| Marginal ulcers | 1 | Cortisone | 1:4 | .. | ... | 1 | .. | Prompt recovery with recurrence |
| Interstitial keratitis (cause unknown) | 1 | Cortisone | 1:4 | .. | ... | 1 | .. | 90% recovery within 6 wk. |
| Interstitial keratitis (syphilitic) | 1 | ACTH | ... | 80-100 | 1,000 | .. | .. | ..... |
| | | Cortisone | ... | 125 | 1,250 | .. | 1 | ..... |
| Unstable corneal scars | 2 | Cortisone locally | 1:4 | .. | ... | .. | 2 | ..... |
| Acute keratitis (unknown cause) | 1 | Cortisone | ... | 75 | 2,000 | .. | 1 | ..... |
| Traumatic corneal ulcer | 1 | Cortisone locally | 1:4 | .. | ... | 1 | .. | Vision lost, however, due to irreparable traumatic intraocular damage |
| Parenchymatous keratitis | 2 | Cortisone locally | 1:4 | .. | ... | .. | 2 | Keratitis inactive; only moderate clearing of scars and vascularity |
| Nonspecific corneal ulcers | 2 | Cortisone locally | 1:4 | .. | ... | 2 | .. | Healing in 24 hr. |
| Exposure keratitis (lupus vulgaris) | 1 | Cortisone locally | 1:4 | .. | ... | 1 | .. | Prompt healing |
| Blood staining of cornea | 1 | Cortisone locally | 1:4 | .. | ... | 1 | .. | Striking improvement |
| Silver nitrate burn of cornea | 1 | Cortisone locally | 1:4 | .. | ... | 1 | .. | No response to penicillin; improvement in 2 days with cortisone |
| Corneal dystrophy | 5 | Cortisone locally | 1:4 | .. | ... | 2 | 3 | In 1 case vision 20/100 R. E., 20/50 + 2 L. E. with corr.; after 2 mo. vision 20/30 O. U. with corr.; improvement equivocal in 2d case |

TABLE 10.—*Miscellaneous Conditions of the Eye*

| Disease | No. of Cases | Drug | Dilution | Dose, Mg. | | Results | | Comment |
|---|---|---|---|---|---|---|---|---|
| | | | | Daily | Total | Improved | Not Improved | |
| Retrolental fibroplasia | 3 | ACTH | ... | 3 | 21-62 | .. | 3 | Treatment at age of 2 mo. in 1 case and at age of 1 mo. in 2 cases |
| Retrolental fibroplasia with glaucoma | 3 | Cortisone, locally | 1:4 | .. | ... | .. | 3 | In all 3 cases pain seemed less and in 2 cases tension normalized; significance doubtful |
| Glaucoma due to hypermature lens | 2 | Cortisone, locally | 1:4 | .. | ... | .. | 2 | Pain less and tension reduced, but not to normal |
| Ocular pain associated with arteriosclerosis | 1 | Cortisone, locally | 1:4 | .. | ... | .. | 1 | No effect on pain |
| Herpes zoster ophthalmicus | 1 | Cortisone, locally | 1:4 | .. | ... | 1 | .. | Iritis controlled rapidly |
| Postoperative hyphema | 1 | ACTH | ... | 50 | 250 | .. | 1 | ..... |
| Cloudy vitreous with retinal detachment? | 1 | ACTH | ... | 50 | 250 | .. | 1 | Vitreous cleared in 2 wk. |
| Severe postoperative reaction | 1 | ACTH | ... | 50 | 250 | 1 | .. | Reaction subsided in 48 hr. |
| Postoperative retained cortex | 2 | Cortisone, locally | 1:1 | .. | ... | 2 | .. | ..... |
| Postoperative cataract infection | 2 | Cortisone, locally and subconjunctivally | 1:4 | .. | ... | 2 | .. | Eye saved, with retention of vision; both patients had antibiotic therapy; evaluation of cortisone therapy difficult |
| Malignant exophthalmos | 2 | Cortisone, locally | 1:4 | .. | ... | 2 | .. | Moderate improvement in exophthalmos and glaucoma; result of treatment equivocal |
| Penetrating wound | 3 | Cortisone, locally | 1:4 | .. | ... | 3 | .. | Rapid subsidence of inflammation |

on the apparent alleviation of pain. In addition, favorable clinical impressions were noted of the therapeutic effect obtained in the several cases of postoperative infection, postoperative retained cortex and penetrating wounds of the eyeball.

## SUMMARY

From this survey, it would appear that the greatest therapeutic efficacy of ACTH and cortisone exists in treatment of the acute exudative inflammatory lesions of the uveal tract, in which they produce a rapid, and frequently dramatic, amelioration of the subjective and objective symptoms of the disease process with recovery, which, at least on a short term basis, is well sustained. Local administration of cortisone in the few cases reported compares favorably with the systemic use of ACTH or cortisone in inflammations of the anterior segment. Chronic inflammations of the uveal tract in general respond less well than do the acute types. Further clinical work is necessary to evaluate the role of these drugs in the therapy of sympathetic ophthalmia.

In such external diseases as episcleritis, sclerokeratitis, phlyctenulosis, dendritic ulcer and rosacea keratitis, the results of local cortisone therapy have been excellent. In a wide variety of other external conditions, such as allergic disorders and marginal ulcer, further clinical experience will probably broaden the therapeutic spectrum of these drugs.

In cases representing a variety of miscellaneous ocular conditions and diseases of the retina and optic nerve, no therapeutic aid was evident.

The results in five typical cases (Donegan) in which the response to treatment with ACTH or cortisone was good are shown photographically in figures 1 to 6.

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# Annual Reviews

## DISEASES OF THE UVEAL TRACT

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THIS REVIEW of the literature extends from July 1949 to October 1950. The attempt was made to secure every article relating to diseases of the uveal tract and abstract it for possible use. Some papers may have been overlooked, or were unavailable. Subsequent reviews will be more inclusive because of the development of bibliographic sources during this year. A few articles published prior to July 1949 are included because of their importance.

### EXPERIMENTAL INVESTIGATIONS

Mörike [1] made actual measurements of the thickness of the choroid in the macular region of human eyes and demonstrated that it possesses a greater thickness in this area. In birds with a double macula the choroid is thicker beneath each macula. He indicates that the metabolism of the macular rods and cones necessitates a greater blood supply—hence the increased thickness of the choroid.

Danforth [2] showed that portions of tissue of the rabbit ciliary body which were transplanted beneath the skin and conjunctiva and introduced into the anterior chamber of another rabbit failed to survive. The tissue transplanted subcutaneously and subconjunctivally had been completely absorbed in one month. The tissue inserted into the anterior chamber became progressively atrophic and was finally replaced by fibrous connective tissue.

MacDonald [3] found two types of ciliary processes in the 6 month old rabbit—a thick and a thin type. After direct exposure to testicular extract for 30 minutes the thick type loses most of its intercellular substance, indicating that this substance is hyaluronic acid. In rabbits given 1 cc. of testicular extract subcutaneously and intraperitoneally twice daily for 20 to 55 days the intercellular substance of the thick process became denser and stained metachromatically, suggesting that the hyaluronic acid was replaced by a sulfated type of mucopolysaccharide. In guinea pigs to which similar injections were given the cells in the epithelial layers of the ciliary body became separated.

Zwiauer [4] studied the retinal and choroidal vessels of albino rabbits under high magnification while they were under the influence of vasodilators, vasoconstrictors and variations in intraocular pressure. The choroidal vessels showed little or no

1. Mörike, K. D.: Comparative Functional Examination in Relation to the Greater Thickness of the Choroid in the Macular Region of the Eye, Klin. Monatsbl. Augenh. **114**:308-319, 1949.

2. Danforth, E. P.: The Fate of Transplanted Ciliary-Body Tissue, Am. J. Ophth. **32**:91-95, 1949.

3. MacDonald, R. K.: Effects of Testicular Extract on Certain Ocular Structures, Am. J. Ophth. **32**:96-101 (June, pt. 2) 1949.

4. Zwiauer, A.: Function of the Choroid, Wien. klin. Wchnschr. **61**:724-725, 1949.

observable spontaneous variation in caliber and no observable response to vasoconstrictors or dilators. They also were more resistant to increases in the intraocular pressure. Circulation persisted even at pressures of 100 to 120 mm. of mercury. The retinal vessels showed spontaneous changes in caliber and reacted promptly to vasoconstrictors and dilators. At pressures of 100 to 120 mm. of mercury the retinal flow was obliterated.

### CONGENITAL ANOMALIES

Callahan [5] reports a family in which the mother and five of her 10 children exhibited bilateral aniridia, hazy corneas, ectopia lentis with cataract, and glaucoma. The eye of one of these patients showed a rudimentary iris, approximately 1 mm. long. It was in contact with the cornea and blocked the filtration angle. One side of the eye showed apparent absence of the canal of Schlemm and the trabeculum. Callahan also reports on a specimen from Dr. T. E. Sanders which showed complete absence of the iris, atrophy of the ciliary body and abnormality of the scleral spur and structures of the anterior chamber angle on one side of the globe. The author states that the glaucoma in his cases may have been due to irritation of the ciliary body by an ectopic lens, closure of the angle by the rudimentary iris and failure of absorption of aqueous due to absence of the iris. The glaucoma in all the cases reported by Callahan showed complete lack of response to pilocarpine, physostigmine and similar drugs, and the surgical procedures carried out were generally inadequate. Cyclodiathermy and goniotomy seemed to be particularly contraindicated.

Falls [6] reports a single family showing a wide variety of pathological changes due to the inheritance of a single dominant gene. It resulted in varying combinations of corneal opacities, embryotoxon, corectopia, pseudopolycoria, slit pupil, iridotasis, dyscoria, ectopia pupillae, ectopia lentis, anterior polar cataract and hydrophthalmia. When gonioscopy could be performed, abnormal tissue was seen to occupy the anterior chamber angle. The glaucoma was difficult to manage, either medically or surgically.

Miosis with poor response of the pupil to mydriatics has been reported in cases of Marfan's syndrome. Sautter [7] examined sections of a portion of iris removed at iridectomy and found absence of the dilator pupillae and relatively little pigment in the iris epithelium.

At times one must distinguish congenital benign melanosis of the iris from heterochromia. Nielsen [8] reports a case of congenital benign melanosis of the sclera and iris. The condition occurred in a dark-haired person, and the hyperpigmentation of the iris produced heterochromia. The author points out that the condition runs an apparently benign course, is unilateral and does not affect the vision. Hemangioma congenitale (nevus flammeus) also may be associated with hyper-

5. Callahan, A.: Aniridia with Ectopia Lentis and Secondary Glaucoma: Genetic, Pathologic, and Surgical Considerations, Am. J. Ophth. **32**:28-40, 1949.

6. Falls, H.: A Gene Producing Various Defects of the Anterior Segment of the Eye, with a Pedigree of a Family, Am. J. Ophth. **32**:41-52, 1949.

7. Sautter, H.: Aplasia of the Dilator Pupillae in Marfan's Syndrome, Klin. Monatsbl. Augenh. **114**:449-453, 1949.

8. Nielsen, E. T.: Congenital Benign Melanosis of the Eye, Acta ophth. **27**:591-597, 1949.

pigmentation of the iris, usually on the affected side,[9] and malignant melanoma of the choroid may be accompanied with small pigmented lesions in the iris, which become hyperpigmented as the tumor develops.[9b]

Anderson [10] presents an interesting pedigree in which three of four siblings and one collateral relative exhibited choroidal sclerosis and pseudoxanthoma elasticum. The fourth sibling had angioid streaks and a retinal lesion resembling retinitis punctata albescens. Of interest is the author's suggestion that angioid streaks, retinitis punctata albescens, choroidal sclerosis, pseudoxanthoma elasticum and retinitis pigmentosa may be due to a failure of the elastic tissues.

### INFLAMMATIONS

Metastatic suppurative forms of uveitis and endophthalmitis seem to be reported less commonly than in former years, probably because of the effectiveness of various drugs and antibiotics in curing systemic infectious diseases. A case of acute uveitis has been reported in the past year [11] in which a culture of staphylococci was obtained from aqueous withdrawn on the fourth day of the disease and intracellular and agglutinated extracellular cocci could be identified in a smear of aqueous withdrawn on the ninth day. In this case the patient exhibited hypersensitivity to an autogenous vaccine prepared from the cultured staphylococci, and the disease subsided after treatment with the vaccine.

#### Endogenous Uveitis

The present concepts of endogenous nonsuppurative uveitis have been covered thoroughly by Woods [12] from the etiological, diagnostic, clinical and therapeutic standpoints. When the ophthalmologist encounters cases of uveitis in his private or clinic practice, he is frequently disturbed at his lack of ability to arrive at a proper etiological diagnosis, and therefore the recommendation of specific treatment. A search of the literature of the past 10 years, and even of the past year, reveals many important advances in the diagnosis and treatment of uveitis. It seems likely at present that the therapeutic approach to the problem of uveitis may prove more fruitful than the diagnostic, for one seems to have reached an impasse in the technics available for the establishment of a diagnosis. Perhaps if more careful studies were made, observable etiological agents might be discovered, such as revelations concerning toxoplasmosis and the recent contribution of Wilder [13] on nematode endophthalmitis.

*Experimental Studies.*—Foss [14] reports the case of a patient with Behcet's syndrome who was hypersensitive in general to cutaneous antigens, especially

9. (*a*) Rosen, E.: Vascular Nevus Associated with Heterochromia, Am. J. Ophth. **33**:107-110, 1950. (*b*) Arjona, L.: Dyschromias of the Iris, Arch. Soc. oftal. hispano-am. **9**:397-404, 1949.

10. Anderson, B.: Familial Central and Peripapillary Choroidal Sclerosis Associated with Familial Pseudoxanthoma Elasticum, Tr. Am. Ophth. Soc. **46**:326-347, 1948.

11. Verrey, F.: Acute Anterior Uveitis Due to Staphylococcus Aureus, Ophthalmologica **118**:461-468, 1949.

12. Woods, A. C.: Endogenous Uveitis: A Manual Prepared for the Use of Graduates in Medicine, Section on Ophthalmology, Home Study Course of the American Academy of Ophthalmology and Oto-Laryngology, 1949.

13. Wilder, H. C.: Nematode Endophthalmitis, Tr. Am. Acad. Ophth. **54**:99-109, 1950.

14. Foss, B.: Experimental Anaphylactic Iridocyclitis, Acta path. et microbiol. Scandinav., 1949, supp. 81, pp. 1-127.

Staphylococcus vaccine. Intradermal injection of this vaccine caused an intense infiltration and was always followed by an attack of uveitis with hypopyon in one to three days. Foss describes primary anaphylactic uveitis in albino rabbits following intravitreal injection of foreign serum or egg albumin, after a constant incubation period. The development of a secondary anaphylactic iridocyclitis in response to these proteins occurs within a few hours after an intravenous injection (provided sensitization had occurred at least eight days before) or within 24 hours after a subcutaneous injection, occasionally in both eyes. An intracutaneous injection does not produce uveitis because the antigen is fixed and does not enter the circulation. Rabbits that have had primary anaphylactic endophthalmitis in one eye will exhibit bilateral anaphylactic iridocyclitis 24 hours after injection of the homologous serum into the other eye. The author terms this reaction sympathetic anaphylactic iridocyclitis, not to be confused with sympathetic ophthalmia. Precipitin tests of the blood showed that antibody formation was greater after intravitreal injection than after intracutaneous injection. The local cutaneous reaction was also much greater after the animal had undergone an attack of primary anaphylactic iridocyclitis. Österlind [15] could not demonstrate any precipitins in the aqueous humor of rabbits one hour after intravenous injection of 2 cc. of horse serum per kilogram of body weight. One-half cubic centimeter of horse serum injected subconjunctivally also resulted in a very low precipitin titer in the aqueous. Subconjunctival injection of hypertonic sodium chloride solution was shown to increase the ability of horse serum to pass from the subconjunctival tissue to the anterior chamber of the rabbit. The subconjunctival injection of 0.5 cc. of horse serum plus an injury to the eye specifically sensitized the uvea, so that subsequent systemic administration of antigen produced iritis. The author points out that if a sufficiently strong antigen concentration is present in the eye, an injury may produce iridocyclitis even in the absence of hypersensitivity.

*General Considerations.*—The value of routine examinations of patients with uveitis has been doubted by many ophthalmologists. It is true that in only a small number of cases is the actual cause determined by this method. Frequently, after exhaustive studies, one must arrive at a possible diagnosis by exclusion or surmise. If one cannot find a specific cause for the uveitis, one has at least excluded a number of important systemic diseases. If a systemic infection should be discovered, the patient has benefited by the survey. In a recent study,[16] Morax made detailed examinations of 252 patients during a period of two years. Of these, 12 per cent had clinical or serologic evidence of syphilis, 5 to 6 per cent had gonorrhea and 18 per cent had focal infections. For the rest of the patients the etiological factor was incompletely understood.

Marchesani [17] believes that information with respect to the pathogenesis and etiology of endogenous uveitis may be obtained by studying its unilateral or bilateral occurrence and the sex and age incidence. It is true that acute uveitis is uncommon

15. Österlind, G.: Experimental Studies into the Pathogenesis of Allergic Inflammation in the Uveal Tract, Acta ophth. **28**:139-162, 1950.

16. Morax, P. P.: Etiological Study and Treatment of Iridocyclitis, with Practical Deductions, Ann. d'ocul. **183**:102-134; 161-198, 1950.

17. Marchesani, O.: Problem of the Endogenous Inflammation of the Eye, Arch. f. Ophth. **149**:69-94, 1949; Unilateral and Bilateral Endogenous Inflammations of the Eye, ibid. **149**:545-561, 1949.

in children, except in association with Still's disease (multiple rheumatoid arthritis), and that rheumatoid uveitis and arthritis are much commoner in males. These observations may eventually prove of value in establishing the cause of some forms of uveitis. Vom Hofe[18] found a higher incidence of extraocular inflammatory disease in patients with uveitis than in control patients.

In another series of cases of uveitis, neurological examination and studies of the spinal fluid were carried out.[19] In six cases of chronic bilateral uveitis sarcoidosis was diagnosed. In four of these the spinal fluid showed pathological alteration. In seven other cases of bilateral uveitis changes were present in the spinal fluid, and in two of these neurological alterations could be demonstrated. In none of the cases had the symptoms lasted more than three or four weeks. It is possible that in a number of cases of acute and chronic uveitis there is a relatively asymptomatic meningoencephalitis, which extends to involve the uveal tract.

Numerous attempts have been made to prove the virus origin of some forms of uveitis by culture of the aqueous humor, choroidal exudates or uveal tissue and by animal inoculation of these materials, without result, except in a few instances (Harada's disease). Braley[20] inoculated mice intracerebrally with aqueous humor from about 20 eyes with uveitis, as well as tissue cultures, but was unable to recover an infectious agent. Ground-up iris and ciliary body tissues from five eyes enucleated because of uveitis were injected intracerebrally into mice, guinea pigs and rabbits. No organism was found.

A study which warrants further investigation, both from a preventive and from a therapeutic standpoint, is that by François,[21] who made gonioscopic examination of the anterior chamber angle in cases of acute iridocyclitis. He first observed congestion of the root of the iris, with edema and exudates in the angle. Pigmentation is usually localized to the lower portion of angle. The edema fluid and cellular exudate may lie in any part of the angle. Organization of the exudate leads to the formation of synechias.

Amsler and Huber[22] have extended the investigations of Verrey and Brückner on the cytology of aqueous exudate in various forms of uveitis. They studied the freshly drawn aqueous, without fixation or staining, by dark field and ultramicroscopic examination. It is possible that further inquiry into the nature of the cells in aqueous exudates may enable one to make a more exact differentiation of the types of uveitis. The scarcity of cells in aqueous after withdrawal, their fragility and the frequent partial decomposition of the structures make cytological studies of little value in some cases.

Gonzáles Pola[23] has shown that in cases of acute uveitis intravenously injected fluorescein penetrates and leaves the anterior chamber rapidly. If the intraocular

18. vom Hofe, K.: Past History and General Susceptibility to Disease of Patients with Uveitis or Keratitis, Arch. f. Ophth. **149**:220-229, 1949.

19. Ljungström, S.: Meningoencephalitis in Chronic Uveitis, Nord. med. **41**:582-585, 1949.

20. Braley, A. E.: Etiology and Treatment of Uveitis, J. Iowa M. Soc. **39**:57-60, 1949.

21. François, J.: Gonioscopic Observations During the Evolution of an Acute Iridocyclitis, Am. J. Ophth. **33**:185-187, 1950.

22. Amsler, M., and Huber, A.: Dark Field and Ultramicroscopic Examinations of the Freshly Drawn Aqueous, Ophthalmologica **118**:450-460, 1950.

23. Gonzáles Pola, A. M.: Hypertensive Uveitis, Arch. Soc. oftal. hispano-am. **10**:215-223, 1950.

pressure rises during an attack of acute uveitis, fluorescein penetrates the chamber rapidly but its elimination is delayed. During the course of chronic uveitis, with increased pressure, fluorescein penetrates the anterior chamber slowly and leaves slowly; and, according to the author, the slower the elimination, the poorer the prognosis.

*Tuberculous Uveitis.*—Little has been added to knowledge of the diagnosis of ocular tuberculosis in the past year. The precepts of Woods have not been improved on by any new diagnostic procedures. That frank ocular tuberculosis continues to be encountered sporadically is attested by two reports. In one case [24] a young man had localized infiltrates in the lung and hilus, with tuberculous peritonitis and suspected meningitis. Within several weeks acute iridocyclitis developed in the left eye, and the iris became studded with yellow nodules. The patient died about three weeks after onset of the iridocyclitis. The pathological changes in the eye were typical of tuberculosis. In another case [25] the right eye of a 4 month old child exhibited pericorneal injection, opacification and edema of the cornea, exudation into the anterior chamber and secondary glaucoma. The mother had exudative pleuritis before the child was born. When the infant was 7 months of age, ulcerative lesions appeared on the skin, with generalized lymphadenopathy and infiltration of the right lung. The eye became atrophic, and granulations protruded through the cornea. The globe was enucleated, and examination showed tuberculous infiltration of the ciliary body with secondary involvement of the cornea.

(*a*) Tuberculous Choroiditis in Miliary Tuberculosis and Tuberculous Meningitis: Tubercles develop in the choroid in many cases of miliary tuberculosis and seem to be very frequent with miliary tuberculosis of the lungs, whether it is associated with tuberculous meningitis or not.[26] Of patients with tuberculous meningitis and without other involvement, about 41 per cent showed choroidal tubercles. The authors believe that an extended period of observation, made possible by streptomycin treatment, brought out changes in the fundus which formerly were not observable. They noted the appearance of fresh tubercles in the choroid in four patients during active streptomycin treatment. Fontana [27] found that the regression of the choroidal tubercles and of papilledema in patients with tuberculous meningitis and disseminated tuberculosis was a valuable prognostic sign of improvement during streptomycin therapy.

Dollfus and Albaugh [28] observed the fundi in cases with choroidal tubercles during treatment with streptomycin. In five cases the tubercles healed with pigmentation after several weeks' treatment. In nine cases the lesions were not modified and the tubercles remained without change after three to four months' treatment, even

24. Semadeni, B.: Tuberculous Panophthalmitis, Ophthalmologica **117**:273-276, 1949.

25. Malesta, C.: Conglomerate Tuberculosis of the Ciliary Body: Report of Rare Cases, Boll. d'ocul. **28**:223-234, 1949.

26. Custodis, E., and Heineman, K.: Retinal Changes in Tuberculous Meningitis and in Miliary Tuberculosis, Klin. Monatsbl. Augenh. **114**:356-363, 1949.

27. Fontana, G.: Ophthalmoscopic Examination of Children with Tuberculous Meningitis and Miliary Tuberculosis Treated with Streptomycin, Arch. ottal. **52**:182-188, 1948.

28. Dollfus, M. A., and Albaugh, C. H.: Fundus Lesions in Tuberculous Meningitis and Miliary Pulmonary Tuberculosis Treated with Streptomycin, Am. J. Ophth. **32**:821-824, 1949.

with administration of 2 Gm. of streptomycin daily. In two cases the tubercles disappeared but the systemic disease progressed and the patients died. In some patients fresh tubercles appeared during treatment, and in others who had been discharged and were later reexamined fresh tubercles were seen. Choroidal tubercles were found in 72 per cent of cases of miliary tuberculosis without meningeal signs and in 40 per cent of cases of tuberculous meningitis.

(*b*) Allergic Tuberculous Uveitis: Gonzáles Pola [29] found that ocular capillary permeability, tested by intravenous injection of fluorescein, was decreased in tuberculous iridocyclitis, especially if a tendency to increased ocular pressure existed. He also found that an intradermal injection of tuberculin tends to decrease the tension in this condition.

Weizenblatt [30] reports the case of a healthy young man who was given a routine tuberculin test. Five days later bilateral neuroretinitis and cyclitis developed. The cutaneous reaction to tuberculin was 4 +. The ocular inflammation eventually subsided. Six and one-half years later another tuberculin test was followed by bilateral neuroretinitis and cyclitis, with eventual complete recovery. The eyes were entirely well between the tests. The author compares this delayed reaction to that sometimes observed in serum disease.

(*c*) Treatment: Woods and Burky [31] and Woods and Wood [32] had shown that promizole® (4,2-diaminophenyl-5′-thiazoylsulfone) has a deterrent action on experimental tuberculosis in the immune-allergic rabbit but is less effective in the nonimmune rabbit. They also showed that streptomycin alone had a markedly deterrent action on the disease in the immune-allergic rabbit and that a combination of streptomycin and promizole® gave an excellent therapeutic result. In a subsequent experiment on the nonimmune rabbit,[33] employing streptomycin and promizole,® they showed a striking clinical difference between the treated and the nontreated animals. The surviving animals were killed 228 days after inoculation and 104 days after cessation of treatment. Cultures of four of six uveas in the treated animal group showed Mycobacterium tuberculosis, and those of two were sterile. Inoculation of the macerated uveas which were positive for tubercle bacilli produced ocular tuberculosis in normal rabbits. The organisms isolated from the uveas by culture were more resistant to streptomycin than those in the uveas of the nontreated group. Histologically, the eyes of four rabbits in the treated group with clinically inactive

29. Gonzáles Pola, A. M.: Etiological Diagnosis of Iridocylitis, Arch. Soc. oftal. hispano-am. **9**:967-973, 1949.

30. Weizenblatt, S.: Allergic Ocular Reaction to the Tuberculin Test: Bilateral Cyclitis and Neuroretinitis, Arch. Ophth. **41**:436-443 (April) 1949.

31. Woods, A. C., and Burky, E. L.: Studies in Experimental Ocular Tuberculosis: X. Effect of "Promine" and "Promizole" in Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, Arch. Ophth. **39**:471-490 (April) 1948; XI. Effect of "Promine" and "Promizole" in Experimental Ocular Tuberculosis in the Normal Rabbit, ibid. **40**:1-13 (July) 1948.

32. Woods, A. C., and Wood, R. M.: Studies in Experimental Ocular Tuberculosis: XII. Effect of Streptomycin and "Promizole" on Experimental Ocular Tuberculosis in the Immune-Allergic Rabbit, Arch. Ophth. **40**:413-432 (Oct.) 1948.

33. Woods, A. C.; Wood, R. M., and Naquin, H. A.: Studies in Experimental Ocular Tuberculosis: XIII. Effect of Streptomycin and Promizole® in Experimental Ocular Tuberculosis in the Normal Rabbit, Arch. Ophth. **43**:834-844 (May) 1950.

tuberculosis showed definite tuberculous lesions. It was later shown [34] that aureomycin had no effect on the course of ocular tuberculosis. Extending these laboratory studies, Woods [35] treated 14 carefully selected patients having ocular tuberculous lesions with streptomycin, 0.5 Gm. every 12 hours, and promizole,® 6 Gm. daily in divided doses. Satisfactory clinical results were obtained with as little as 26 Gm. of streptomycin and 156 Gm. of promizole.® The author decided that a total dose of 42 Gm. of streptomycin should be satisfactory in all but cases of especially severe and resistant disease. In all the patients there was excellent control of the clinical activity and inflammation. Toxic symptoms occurred in a large percentage of patients but disappeared rapidly without complications if the drugs were withdrawn.

Bietti [36] shows that paraaminosalicylic acid acts as a bacteriostatic agent in the control of experimental ocular tuberculosis in rabbits and guinea pigs and has a greater effect when combined with streptomycin. When given in prophylactic doses, these drugs do not prevent onset of the disease. He treated 18 patients having ocular tuberculosis with 0.5 Gm. of streptomycin and 10 to 15 Gm. of paraaminosalicylic acid daily for 20 days, with good results. Paraaminosalicylic acid was used, with satisfactory results, in two cases of diffuse uveitis, two cases of disseminated chorioretinitis, one case of anterior uveitis with sclerosing keratitis and one case of papilloretinitis. A failure occurred in the treatment of a tuberculoma of the ciliary body and choroid.

In another experiment on rabbits [37] subconjunctival administration of streptomycin in a daily dose of 30 mg. for 17 days did not benefit the experimental tuberculosis. The authors found no difference between the effect of streptomycin alone and that of a combination of streptomycin and glucosulfone sodium (promine®) on experimental ocular tuberculosis and indicate that there was no demonstrable synergism between streptomycin and glucosulfone sodium.

*Ocular Sarcoidosis.*—Woods [38] states that iritis is the most frequent and important of all ocular lesions of sarcoidosis and that the characteristic picture is a nodular iritis which is painless and accompanied with only slight inflammatory signs. Sarcoid nodules are larger, pinker and more vascular than miliary tubercles. "Mutton fat" keratic precipitates are common, and Koeppe nodules in the peripheral iris are often present. In occasional cases the condition is more acute, with heavy plastic exudates and more violent inflammation and pain. The course of the disease is chronic, with minor exacerbations and remissions. The lesions heal by

34. Woods, A. C.; Wood, R. M., and Naquin, H. A.: Studies in Experimental Ocular Tuberculosis: XIV. Failure of Aureomycin to Affect the Course of Ocular Tuberculosis, Arch. Ophth. **43**:845-848 (May) 1950.

35. Woods, A. C.: Therapeutic Action of Streptomycin and Promizole® in Clinical Ocular Tuberculosis, Arch. Ophth. **42**:521-537 (Nov.) 1949.

36. Bietti, G. B.: Preliminary Experimental Investigation and Clinical Observations Concerning the Effect of Paraaminosalicylic Acid on Ocular Tuberculosis, Boll. d'ocul. **28**:449-470, 1949; Use of Paraaminosalicylic Acid Alone or in Association with Streptomycin in Ocular Tuberculosis, Arch. Ophth. **43**:431-445 (March) 1950.

37. Macaskill, J., and Weatherall, M.: Streptomycin and Promizole in Experimental Ocular Tuberculosis, Brit. J. Ophth. **34**:147-155, 1950.

38. Woods, A. C.: Sarcoidosis: The Systemic and Ocular Manifestations, Tr. Am. Acad. Ophth. **53**:333-343, 1949.

hyalinization of the nodules or by complete regression, leaving small areas of fibrosis. Parotitis may occur along with the uveitis, and systemic lesions of sarcoidosis may appear. The diagnosis and differential diagnosis may be difficult.[39] Tuberculosis, Hodgkin's disease (lymphogranulomatosis), syphilis, neoplasm, silicosis, leukemia, leprosy and other forms of lymphoblastoma must be excluded. Important for a correct diagnosis are the history; clinical evidence of disease simulating sarcoidosis; a negative tuberculin reaction; characteristic pulmonary, cutaneous or osseous lesions; changes characteristic of sarcoidosis in biopsy specimens of the skin or lymph nodes, and elevation of the blood globulin. Rosenthal[40] reports a case in which almost every tissue in the body was involved, including the eyes. At autopsy vascular changes were seen to be common and widespread, consisting of panarteritis and periarteritis (hypertensive vascular disease was present, and the specificity of these lesions is doubtful). An interesting observation was that the intradermal or intraperitoneal injection of an extract of emulsified hilar lymph node in animals resulted in the development of a positive cutaneous reaction to tuberculin. Intradermal inoculation produced a local infiltration, which lasted six weeks, but biopsy of the infiltrative area showed no specific pathologic changes. On the death of the animals, six weeks after inoculation, microscopic sections of the lymph nodes, liver, spleen and lungs were suggestive of sarcoidosis, but cultures were sterile and tubercle bacilli were not found in the sections.

Landers[41] described discrete grayish white bodies in the most dependent portion of the vitreous in patients with uveitis due to sarcoidosis. These bodies showed no change in size, number or character over an observation period of three months, even though the uveitis had become quiescent in all cases. These bodies were found in five eyes of three patients affected, and in five other eyes they were not apparent.

(*a*) Treatment: Woods and Landers have indicated that nitrogen mustard (methyl-*bis* or *tris* [2-chloroethyl] amine) therapy has no important permanent effect on the lesions of Boeck's sarcoidosis.

Curtis and Grekin[42] treated four patients with sarcoidosis having ocular involvement with dihydrotachysterol, 3.75 mg. being given daily for three days and then 1.24 mg. daily. At times the drug was combined with calciferol U. S. P. in daily doses equivalent to 150,000 to 300,000 U. S. P. units of vitamin D. Three of the patients were treated with calciferol alone. The disease became inactive in two patients, and there was some improvement in the third. One patient was treated with both drugs and showed objective and subjective improvement. The authors based this treatment on the observation that dihydrotachysterol produces an increased excretion of phosphorus. A loss of phosphorus from the body may cause a breakdown of phospholipids, which stimulate the production of epithelioid cells.

39. Gifford, B. L., and Krause, A. C.: Differential Diagnosis of Boeck's Sarcoidosis, Arch. Ophth. **41**:667-696 (June) 1949.

40. Rosenthal, S. R.: Pathological and Experimental Studies on Boeck's Sarcoid: I. Report of a Case with Panarteritis, Periarteritis, Terminal Hypertension and Uremia, and the Reproduction of a Sarcoid-Like Lesion in Guinea Pigs, Am. Rev. Tuberc. **60**:236-248, 1949.

41. Landers, P. H.: Vitreous Lesions Observed in Boeck's Sarcoid, Am. J. Ophth. **32**:1740-1741, 1949.

42. Curtis, A. C., and Grekin, R. H.: Sarcoidosis: IV. Treatment with Calciferol and Dihydrotachysterol, Tr. Am. Acad. Ophth. **53**:344, 1949.

*Syphilitic Uveitis.*—An important study [43] was made of the charts of patients with known ocular syphilis in three hospitals in New York city where the treatment of ophthalmic patients is carried out. The charts of 467 patients were analyzed; 87 cases of uveitis were recorded. In hospital A, 5 of 57 patients, and in hospital B, 16 of 247 patients were treated with penicillin; in hospital C, 5 of 163 patients received penicillin, and 27 received penicillin and other antisyphilitic drugs. The comparative infrequency with which penicillin is used in treatment of ocular syphilis may be due to the doubt concerning its efficacy, especially in interstitial keratitis. This probably is not true of uveitis, since there are reports of success with this antibiotic.[44] The authors comment on the incompleteness of the histories and of the follow-up study in many cases which were reviewed.

Harrington and Henry [44c] state that it is important to initiate penicillin treatment cautiously in patients with syphilitic uveitis, beginning with 5,000 to 10,000 units for the first four to six doses and then increasing the dose rapidly to 50,000 units. All patients should be followed, because of the danger of relapse.

Harley and Mather [45] reported the findings in a premature Negro female in whom a lesion resembling retrolental fibroplasia developed at the age of 6 weeks. At 7 weeks the lesion had extended to involve the entire periphery of each retina, and the veins were moderately dilated. The patient's blood was strongly positive in the Kolmer, Kahn and Mazzini tests, and the mother's blood gave a negative serologic reaction. The infant died of pneumonitis, and necropsy showed an inflammatory process in the entire periphery of the choroid, which was considerably thickened. The retina was slightly separated by fluid but was otherwise normal. The authors comment on Stokes's finding that 21 per cent of mothers of syphilitic children show no evidence of the disease on ordinary clinical and serologic examination.

*Ocular Leprosy.*—The one report on ocular leprosy [46] concerns treatment with diaminodiphenylsulfone. Twenty-five patients were treated. This drug prevented the severe uveal complications of leprosy but was incapable of arresting the slowly progressive lesions. If the cornea alone is affected, the drug hastens the absorption of corneal infiltrates; but if the iris and ciliary body are involved, the progress of the disease is not arrested.

*Sympathetic Ophthalmia.*—Experimental Studies: Collins [47] attempted to sensitize guinea pigs to beef uvea by intraperitoneal and intramuscular injections of macerated whole beef uvea and adjuvants. After three months the animals were killed. One animal showed involvement of both eyes, and the lesions were similar to those of sympathetic ophthalmia.

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43. Payne, B. F.; Goldberg, J. A., and Simonton, J. T.: Clinical Management of Ocular Syphilis, Am. J. Ophth. **33**:605-610, 1950.

44. (*a*) Cannizzo, E. G.: Effect of Penicillin on Syphilitic Uveitis, Boll. d'ocul. **28**:555-562, 1949. (*b*) Alvarez, A. A.: Late Syphilitic Uveitis Healed by Penicillin in Massive Subconjunctival Injections, Ann. d'ocul. **182**:521-524, 1949. (*c*) Harrington, D. O., and Henry R.: Present Concept of the Therapy of Ocular Syphilis, Am. J. Ophth. **32**:806-812, 1949.

45. Harley, R. D., and Mather, R. W.: Peripheral Choroiditis Simulating Retrolental Fibroplasia, Am. J. Ophth. **33**:1417-1420, 1950.

46. Urrets Zavalia, A.: Action of Diaminodiphenylsulfone on Ocular Complications of Leprosy, Arch. Soc. oftal. hispano-am. **9**:160-175, 1949.

47. Collins, R.: Experimental Studies on Sympathetic Ophthalmia, Am. J. Ophth. **32**:1687-1699, 1949.

In a second series he used a mixture of homologous guinea pig uvea, liquid petrolatum U. S. P., an oxycholesterol-petrolatum ointment base (aquaphor®) and heat-killed tubercle bacilli. The guinea pigs were given 0.5 cc. of the mixture weekly for three doses, and a fourth dose was given at the end of five weeks. After three to six months the animals were killed. In 12 of the 25 guinea pigs a lesion resembling sympathetic inflammation was present in the uvea. Nineteen control guinea pigs received the same injection of adjuvant (aquaphor,® liquid petrolatum and heat-killed tubercle bacilli) together with an equivalent of albino guinea pig liver. None of the control animals showed choroidal lesions or other reticuloendothelial involvement.

Schreck [48] studied both eyes, the optic nerves and the chiasm of a patient with sympathetic ophthalmia who died of a brain tumor. He observed a migrating perivasculitis and perineuritis, which to him confirmed the uninterrupted progression of the specific process from the exciting to the sympathizing eye across the chiasm. In the sections he noted a microbiologic agent, similar in size, shape and staining properties to a Rickettsia. The rickettsias, called Rickettsia liquoritropica migrans by the author, were also observed in the connecting pathways. The Rickettsia was apparently present in the conjunctival sac as a saprophyte and could be demonstrated both in the epithelium and subepithelially. It produced the syndrome of sympathetic ophthalmia when introduced into the interior of the eye. Inoculation of the vitreous or anterior chamber of experimental animals with uvea and aqueous humor from the exciting and sympathizing eyes in cases of human disease, after opening the capsule of the lens, produced sympathetic ophthalmia without fail. In the inoculation of the vitreous of chicks the pecten was of decisive importance for the emigration into the second eye. The author cites investigations as yet unpublished in which he transmitted sympathetic ophthalmia from the human eye to the eye of chicks and in continuous transfer from chick to chick eye, for at least six passages. The Rickettsia could be cultivated on the chorioallantois of the developing chick embryo, either from uveal tissue or from aqueous humor. Intranasal vaccination of mice and rats with uveal tissue or aqueous from the human or chick eye with sympathetic ophthalmia produced chronic bronchopneumonia. Swallowed material led to invasion of the epithelium of the intestine and perivasculitis of the liver. Intracerebral inoculation of mice produced perivasculitis with demonstrable rickettsias and chronic uveitis. To the author, this unequivocal proof of the etiological part of the rickettsias in sympathetic uveitis is important in diagnosis, since aspiration of aqueous from an eye suspected of being infected and immediate inoculation of the chick embryo should give proof of the disease in two days.

Clinical Aspects: Joy [49] analyzed 436 cases of sympathetic ophthalmia and found that in about 85 per cent the condition was the result of perforating wound of the eye. Sixty-five per cent of these wounds were of accidental origin, and 20 per cent followed surgical procedures. From a prophylactic standpoint, he found that if vision is reduced to light perception in the injured eye and is good in the fellow

48. Schreck, E.: Clinical Manifestations, Microbiology and Pathology of Sympathetic Ophthalmia, Arch. f. Ophth. **149**:656-679, 1949; Etiology of Sympathetic Ophthalmia, Klin. Wchnschr. **28**:423-424, 1950.

49. Joy, H. H.: The Clinical Aspects of Sympathetic Ophthalmia, Am. J. Ophth. **32**:1383-1389, 1949.

eye enucleation is indicated (1) when the patient cannot be controlled, (2) when the tension is low and there is ciliary injection for as long as three weeks and (3) when there are extensive wounds of the ciliary body with prolapse of the uvea and vitreous. Reports of the value of early enucleation after onset of sympathetic ophthalmia are at variance. Fischer [50] reports 28 cases, in 12 of which all vision was lost in spite of early enucleation of the injured eye. On the other hand, Österlind [51] reported five cases in which immediate enucleation was done, with good results. McPherson [52] reports 61 cases. In two instances the disease developed after enucleation of the exciting eye. Of 20 cases in which enucleation was performed within seven days of the onset of sympathetic ophthalmia, a final visual acuity of 20/100 or better was obtained in 60 per cent. Of 25 cases in which enucleation was performed more than seven days after onset, a final visual acuity of 20/100 or better was obtained in only 24 per cent. Of the 11 cases in which enucleation was not performed, final visual acuity of 20/100 or better was obtained in 2. His findings seem to indicate that early enucleation is important in sympathetic ophthalmia.

*Toxoplasmosis.*—In a symposium on toxoplasmosis at the annual meeting of the American Academy of Ophthalmology and Otolaryngology in 1949, it was reported [53] that in approximately 78 reported cases of congenital human toxoplasmosis with associated chorioretinitis the diagnosis was considered proved or probable. In these 78 cases, 33 eyes showed a macular type of chorioretinitis and 34 both macular and extramacular foci. Twenty-two eyes showed one or more lesions not involving the macula. The site and character of the lesions in the remaining 67 eyes were not indicated. Thirty-four eyes exhibited acute chorioretinitis, and 64, healed chorioretinitis. Microphthalmos was present in 37 eyes, and optic nerve atrophy, in 33 eyes. Chorioretinitis in various stages of activity is the most prominent ocular manifestation of toxoplasmosis and is almost always bilateral.

Sabin [54] points out the difference between the pathological effects of toxoplasmic infection in prenatal life and those in adults and indicates the great susceptibility of the fetal central nervous system. He showed that the neutralizing antibody test, which formerly was used in the diagnosis of this disease, gave only qualitative information and did not serve to differentiate between the toxoplasmic "antibody" in the serum of the normal person and that in the serum of a mother or child proved to be infected. The methylene blue dye test of Sabin and Feldman is more quantitative and differentiates "normal" human serums from those which are pathological. The titer in cases of proved infections in experimental animals and human subjects is often in the range of 1 : 1,000 to 1 : 16,000. The titer of "normal" serums rarely exceeds 1 : 64. In experimental animals the dye test antibody appears

50. Fischer, E.: Twenty-Eight Cases of Sympathetic Ophthalmia: Report of 28 Cases, Arch. Soc. oftal. hispano-am. **9**:850-860, 1949.

51. Österlind, G.: Considerations on the Treatment of Sympathetic Ophthalmitis in the Initial Stage, Acta ophth. **28**:133-137, 1950.

52. McPherson, S. D., Jr.: Sympathetic Ophthalmia; A Review of 61 cases, South. M. J. **42**:120-124, 1949.

53. Hogan, M. J.: Toxoplasmosis: Ocular Manifestations, Tr. Am. Acad. Ophth. **54**:183-189, 1950.

54. Sabin, A. B.: Toxoplasmosis: Diagnosis and Treatment, Tr. Am. Acad. Ophth. **54**:190-204, 1950.

three to five days after inoculation with Toxoplasma and reaches peak titers [54a] of 1:1,000 to 1:4,000 in 10 to 21 days. Complement-fixing antibody [55] appears later and may be absent three to four weeks after onset of an infection. Both these antibodies may persist, however, in high titer for months or years; so it is not possible to say that a high titer of either antibody is indicative of an active or a persistent infection. Forty-three children who exhibited chorioretinopathy associated with other evidence of cerebral damage were studied.[56] Two groups of children were found, one serologically compatible with a diagnosis of congenital toxoplasmosis and the other without serologic evidence of the disease. The 20 children in the first group all had dye test titers of 1:1,024 to 1:16,384, and all but two had complement-fixing titers of 1:16 to 1:128. In the second group of 20 children the dye and complement fixation titers were negative for toxoplasmosis. The mothers of these children showed very low titers. The authors conclude that there is another syndrome, not related to toxoplasmosis, and probably of more frequent occurrence, in which chorioretinopathy is one manifestation. If the chorioretinopathy of presumable congenital origin is associated with cerebral calcification, the chances are approximately 9:1 that serologic tests will prove it due to toxoplasmosis. The ocular and cerebral manifestations in the group which does not have toxoplasmosis are probably due to a developmental defect, rather than to healed inflammatory foci. The skin test for toxoplasmosis is probably of value only in population surveys and is therefore merely of qualitative value. The incidence of toxoplasmin sensitivity in a group of young persons was 10 per cent and in a group of older patients 28 per cent. Of patients with chorioretinitis, 71 per cent, and of 40 patients with anterior uveitis 33 per cent, were sensitive to toxoplasmin.[57]

*Rheumatoid Uveitis.*—Godtfredsen [58] describes two types of joint disease which may have associated ocular lesions. The first type comprises the acute arthritides, such as rheumatic fever, gonorrheal arthritis, Reiter's disease and gout. The second type comprises forms of chronic joint disease, such as rheumatoid arthritis (chronic primary arthritis), Still's disease and Marie-Strümpell disease (rheumatoid arthritis of the spine).

Acute rheumatic fever and gonorrheal arthritis were accompanied with iritis in 4 to 5 per cent of cases. Reiter's disease was accompanied with iritis in 10 per cent, and gout, in 2 per cent. Iritis occurred in rheumatoid arthritis in 2.5 per cent, in Still's disease in 20 per cent and in Marie-Strümpell disease in 15 to 56 per cent of cases. In acute arthritic disease the iritis is acute and serous (nongranulomatous), and in chronic joint disease it is chronic with irregular acute exacerbations. The antistreptolysin titer was increased in 80 per cent of cases of

54a. The dye test titer is the highest original dilution of a serum which, in the presence of a constant amount of accessory factor, is capable of depriving the cytoplasm of 50 per cent of the toxoplasmas of their affinity for methylene blue at $p_H$ 11.0.

55. Sabin, A. B.: Complement Fixation Test in Toxoplasmosis and Persistence of the Antibody in Human Beings, Pediatrics **4**:443-453, 1949.

56. Sabin, A. B., and Feldman, H. S.: Chorioretinopathy Associated with Other Evidence of Cerebral Damage in Childhood: A Syndrome of Unknown Etiology Separable from Congenital Toxoplasmosis, J. Pediat. **35**:296-309, 1949.

57. Frenkel, J. K.: Uveitis and Toxoplasmin Sensitivity, Am. J. Ophth. **32**:127-133 (June, pt. 2) 1949.

58. Godtfredsen, E.: Pathogenesis of Concurrent Eye and Joint Disease, Brit. J. Ophth. **33**:261-270, 1949.

acute rheumatic fever, indicating to the author that this disease is an allergic-toxic reaction to an infection with hemolytic streptococci. He points out the resemblance of Still's disease, Reiter's disease, rheumatoid arthritis and Sjögren's syndrome to Stevens-Johnson disease, Behcet's syndrome and disseminated lupus erythematosis in their multiple sites of involvement. Still's disease is essentially rheumatoid arthritis of childhood, and in the original report by Still ocular lesions were not described.[59] A quiet chronic iritis is commonly seen, and synechias, complicated cataract and a band-shaped opacity of the cornea may develop. Iridocyclitis develops early, and in one instance it preceded onset of the arthritis.

In 1937 Mester observed a relative leukopenia after subcutaneous injection of 1 cc. of 0.1 per cent salicylic acid solution in patients with rheumatic infections. This test is done 12 hours after a meal. Five white blood cell counts are made, and the average is compared with an equal number of counts done 30 to 60 minutes after injection of 1 cc. of 0.15 per cent salicylic acid solution, divided into five wheals, each containing 0.2 cc. of solution. A 10 per cent decrease in the leukocyte count is considered a negative response; a 10 to 15 per cent decrease, a questionable result, and more than a 30 per cent decrease, a strongly positive reaction. Pasca [60] found 28 strongly positive responses in 50 patients with possible rheumatic disease of the eyes. Of 10 patients with unquestionable rheumatic disease, the response to the test was positive in nine, and in 27 patients with nonrheumatic ocular disease the response was negative. In 10 patients with probable tuberculous disease of the eyes the result was negative.

*Harada and Vogt-Koyanagi Disease.*—It is not certain whether these two conditions should be considered separate entities. In many cases there are features common to both diseases, and at times the early stages of involvement may resemble one type and the later stages assume features of the other type. Patients having only involvement of the posterior uveal tract of both eyes may manifest systemic lesions characteristic of the Vogt-Koyanagi syndrome. The changes in the skin in these two conditions are similar to those in some cases of sympathetic ophthalmia. It is probable that these disorders are due to a virus, and some experimental work (Takahashi; Tagami; Malbrán, and Muhlmann) supports this thesis. However, a number of cases have been reported in which the spinal fluid, aqueous humor and subchoroidal fluid did not show evidence of a virus on culture or animal inoculation.[61] The condition described by Busacca [62] may be related to this group of cases of uveitis. The case described by Gittler [63] is important, for it belongs to this group and shows the histological changes in the fairly early stages of the disease. The patient had uveitis of the left eye periodically for six months, with severe headache, dizziness, ringing of the ears, nausea and vomiting. Detachment of the retina occurred, and enucleation was done because of a suspected tumor. Two

59. Golden, C.: Ocular Defects of Still's Disease, Proc. Roy. Soc. Med. **42**:755-762, 1949.

60. Pasca, G.: Value of Mester's Reaction in Diagnosis of Ocular Manifestations of Possibly Rheumatic Origin, Boll. d'ocul. **27**:439-455, 1948.

61. Bruno, M. G., and McPherson, S. D., Jr.: Harada's Disease, Am. J. Ophth. **32**:513-522, 1949.

62. Busacca, A.: A Form of Chorioretinitis with Retinal Detachment, Arch. d'opht. **9**:549-583, 1949.

63. Gittler, R.: Histological Changes in Bilateral Choroidal Detachment of Inflammatory Origin, Klin. Monatsbl. Augenh. **115**:333-338, 1949.

months later the opposite eye was similarly affected, with final reattachment of the retina and vision of 6/8 with correction. Three months later iridocyclitis developed but healed without visual loss. The enucleated eye showed an extensive choroidal detachment, from the ora serrata to the disk, on the nasal side and to 4 disk diameters from the disk temporally. The choroid was greatly thickened by exudate and diffuse round cell infiltration, and the disk was edematous. The retina showed a moderate detachment from the choroid but was not inflamed. No vascular changes were present.

*Recurrent Iritis with Hypopyon (Behcet's Syndrome).*—This clinical entity is characterized by (1) recurrent iritis with hypopyon, (2) aphthous ulcers of the buccal cavity and genitalia, (3) ulcus vulvum acutum (Lipschütz), (4) thrombophlebitis of the fundus and extremities, (5) nodular erythemas of the skin and (6) arthralgias. The articular lesions are characterized by intermittent hydrarthrosis of the larger joints and phalanges or an arthralgia which is migrating and unaccompanied with fever.[64] The cutaneous eruption consists of papules or vesiculopustules on the genitalia, which ulcerate and are painful. The thrombophlebitis appears suddenly in the extremities and may also affect the choroid or retina. The etiological factor is unknown, and cultures and animal inoculation of the aqueous humor have shown no organisms.

*Leptospiral Uveitis.*—Hanno and Cleveland[65] state that involvement of the anterior uveal tract is variously reported as occurring in from 3 to 44 per cent of cases of leptospirosis. The posterior uveal tract is rarely involved.

Weil's disease (spirochetal jaundice) has been reported only 222 times in the United States literature. Human infection occurs from contact with stagnant waters, contaminated with murine excreta, and the portal of entry is the abraded skin, the gastrointestinal tract, the nasal mucosa or the conjunctiva. Headache, fever, prostration and myalgia, and in severe cases jaundice, hemorrhagic phenomena and renal impairment, are the common symptoms and signs. The diagnosis is made by isolation of the organism from the blood and urine or by demonstration of specific agglutinins in the serum. Agglutination in a titer of 1 : 300 or above or a complement fixation titer of 2 units or more is considered diagnostic. Penicillin is a specific therapeutic agent. These authors report the case of a 26 year old Negro sewer worker who acquired spirochetal jaundice. Bilateral iridocyclitis developed one month after onset of the disease and responded to penicillin therapy.

Wood and Chesney had demonstrated that macerated uveal tissue from horses with periodic ophthalmia, after Berkefeld filtration, was infective for rabbits, and that after six transfers in rabbits it could reproduce the disease in normal horses. Cultures of these filtrates were bacteriologically sterile. Other workers had demonstrated evidence of a connection between periodic ophthalmia and leptospirosis. Wood and Davis[66] examined the serums of 30 normal horses and of 17 horses affected with periodic ophthalmia for Leptospira agglutinins. They were found in

64. Adamantiades, B., and Locando, N.: The Complex Syndrome of Recurrent Uveitis Known as the Syndrome of Behcet, Presse méd. **57**:501-503, 1949. Ferrata, L., and Montanelli, M.: Etiology of Recurrent Uveitis with Hypopyon, Ann. ottal. e. clin. ocul. **75**:10-19, 1949.

65. Hanno, H. A., and Cleveland, A. F.: Leptospiral Uveitis, Am. J. Ophth. **32**:1564-1566, 1949.

66. Wood, R., and Davis, G.: Correlation of Periodic Ophthalmia with Leptospira Agglutinins in Horses, Am. J. Ophth. **33**:961-962, 1950.

high titer in 94 per cent of horses with clinical evidence of periodic ophthalmia and in 13 per cent of normal horses.

*Treatment of Uveitis.*—The treatment of various forms of uveitis by specific and nonspecific means has been adequately reviewed by Leopold.[67]

ACTH and Cortisone: There is evidence that both the pituitary adrenocorticotropic hormone (ACTH) and cortisone administered parenterally exert a rapid and beneficial effect on both the symptoms and the inflammatory process of acute iridocyclitis and choroiditis,[68] provided the patient shows a satisfactory adrenal response. Some physiological side effects, such as hypertension, glycosuria and a tendency to development of Cushing's syndrome, occur with the treatment, but these effects are reversible on withdrawal of the medication. In some instances acute inflammations may be entirely healed in seven to 10 days but are followed by a relapse when treatment is stopped. In other cases the relapse does not occur. Chronic ocular inflammations respond poorly and relapse on cessation of treatment.

In two reports,[69] seven patients with acute iridocyclitis were treated with ACTH and six with cortisone. The disease was severe in each case, and nine patients had failed to respond to the usual measures. The patients noted rapid relief from pain (in four hours), except for one, who was better in 24 hours. Within 45 minutes to 24 hours smaller or greater amounts of fibrin had disappeared from the anterior chamber. In no case was an aqueous flare present after 48 hours. In three eyes the anterior chamber was free of cells in three days, and in 10 eyes, in four to 12 days. One eye failed to respond completely after 14 days' treatment. Secondary glaucoma was present in four eyes and subsided in four hours to four days. One patient treated with ACTH had recurrence in two months and then responded equally well to cortisone. Seventeen days later a mild relapse occurred, which responded permanently to topical use of cortisone.

Three of five patients with acute choroiditis who were treated with ACTH had recurrent lesions, and two had failed to respond to previous general therapy. In each patient the response to ACTH was definite, with subsidence of the aqueous flare and cellular reaction, clearing of vitreous opacities, regression of edema and decrease in size of the scotoma, as demonstrated by studies of the central fields. Three patients had no relapse in the four to eight weeks after treatment during which they were followed. Two patients with acute diffuse uveitis were treated, one with ACTH and one with cortisone. Each responded rapidly to therapy, and one had had no recurrence in two months and the other in three weeks.

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67. Leopold, I. H.: Annual Review of Pharmacology and Toxicology of the Eye: Review of the Literature, Arch. Ophth. **44**:300-348 (Aug.) 1950.

68. (*a*) Mann, W. A., and Markson, D. E.: A Case of Recurrent Iritis and Episcleritis on a Rheumatic Basis Treated with ACTH, Am. J. Ophth. **33**:459, 1950. (*b*) Olson, J. A.; Steffensen, E. H.; Margulis, R. R.; Smith, R. W., and Whitney, E. L.: Effect of ACTH on Certain Inflammatory Diseases of the Eye, J. A. M. A. **142**:1276-1278 (April 22) 1950. (*c*) Woods, A. C.: Clinical and Experimental Observation on the Use of ACTH and Cortisone in Ocular Inflammatory Disease, Am. J. Ophth. **32**:1325-1348, 1950. (*d*) Gordon, D. M., and McLean, J. M.: ACTH in Ophthalmologic Conditions, J. A. M. A. **142**:1270-1276 (April 22) 1950.

69. (*a*) Olson, J. A.; Steffensen, E. H.; Smith, R. W.; Margulis, R. R., and Whitney, E. L.: Use of Adrenocorticotropic Hormone and Cortisone in Ocular Disease, Tr. Sect. Ophth., A. M. A., 1950, to be published. (*b*) Steffensen, E. H.; Olson, J. A.; Margulis, R. R.; Smith, R. W., and Whitney, E. L.: The Experimental Use of Cortisone in Inflammatory Eye Disease, Am. J. Ophth. **33**:1033-1040, 1950.

Five patients with chronic iridocyclitis were treated with ACTH. One of these had rheumatoid uveitis; one had sarcoidosis, and the cause in the others was unknown. In all patients a gradual improvement occurred, and in two the lesion completely resolved. A recurrence developed in all within one to 10 weeks after cessation of treatment. These results of treatment of chronic iridocyclitis are borne out by our studies,[70] in which a beneficial effect was noted but an incomplete regression of the iridocyclitis occurred. Two patients with acute central chorioretinitis were treated with ACTH. The edema and swelling subsided, with improvement in vision; but within a week after discontinuation of treatment the lesions again became active.

The results from topically applied cortisone are surprising in view of the low solubility of the drug. There is evidence [71] that it is effective in some forms of iridocyclitis. Woods found improvement of the ocular inflammation in the patients he treated, and in two cases of uveitis complicated by glaucoma the tension was controlled. He also showed that cortisone prevented the ocular anaphylactic reaction to horse serum and beta hemolytic streptococci in sensitized animals. Both ATCH and cortisone were also shown to prevent the focal reaction to tuberculin given subcutaneously in immune-allergic rabbits with ocular tuberculosis. The intraocular inflammation resulting from injection of jequirity and glycerin were also prevented when cortisone was administered with these substances.

Leopold and associates [72] show that intramuscular injection of tripelennamine has no therapeutic effect in established experimental uveitis. In two reports [73] evidence is presented that aureomycin has a beneficial effect in some cases of iridocyclitis.

### TRAUMATIC DISEASES

The term "rupture of the choroid" refers to two heterogeneous morbid states, according to Tower [74]: disruption of the choroid due to direct injury and that due to indirect injury. In the latter the trauma is produced by contrecoup, resulting in single or multiple breaks of various sizes in the region of the disk and concentric to its edge. The author is inclined to favor the theory that the changes in the choroid are produced by necrosis rather than actual disruption and are due to trophic alterations resulting from obstruction of the posterior ciliary arteries. The obstruction may be caused by vascular reflexes due to injury.

### CIRCULATORY DISEASES

*Anatomy of the Uveal Vessels.*—The arrangement of the elastic fibers in the retinal and choroidal vessels differs in that one well defined internal elastic layer is present in the choroidal arteries, whereas in the retinal arterioles the elastic

70. Hogan, M. J.; Engleman, E. P., and Thygeson, P.: Effects of Cortisone and ACTH on Ocular Disease, Proc. Soc. Research Ophth., to be published.

71. Woods.[68c] Olson and others.[68a] Steffensen and others.[69b]

72. (*a*) Leopold, I. H.; Dean, W., and Blazar, H.: An Evaluation of an Antihistaminic Drug in Experimental Uveitis, Am. J. Ophth. **32**:31-34, 1949. (*b*) Braley, A. E., and Sanders, M.: Aureomycin in Ocular Infections: A Study of Its Spectrum, ibid. **32**:119-127, 1949.

73. Braley and Sanders.[72b] Bellows, J. G.; Richardson, V. M., and Farmer, C. J.: Aureomycin in Ophthalmology, Am. J. Ophth. **33**:273-282, 1950.

74. Tower, P.: Traumatic Choroiditis: Review of Literature and Report of 10 Cases, Arch. Ophth. **41**:341-352 (March) 1949.

elements form a scaffolding between and around the muscle cells of the vessel wall. In the iris the latter arrangement is present to some extent. The arteries in choroidal tumors show the same elastic tissue arrangement as in the normal choroid.[75]

Loewenstein[76] demonstrated the large epithelial type of glomus cells in the arterial walls of the choroidal vessels. These cells are responsible for closure of the shunts which may exist between small arteries and veins to eliminate the capillary system. The cells were absent in the anterior portion of the choroid.

Pagliarani[77] reports the histological changes in the eye of a newborn infant who died of fetal erythroblastosis. The ocular tissues showed pronounced hyperplasia of the mesenchymal elements and of the endothelial cells. There was some degeneration and separation of the retinal pigment epithelium cells.

McCulloch[78] describes the pathological changes in the eyes of two patients known to have the symptoms and ophthalmoscopic signs characteristic of choroideremia. Both patients had been blind for approximately 20 years prior to death. One of the four eyes showed changes in the anterior and posterior segments as a result of glaucoma. The vessels of the anterior portion of the eye and the long and short posterior ciliary vessels outside the eyeball showed no abnormal reduction in caliber. The principal changes in the eyes occurred in the choroid and were characterized by an extreme degree of atrophy. In some areas the choroid had completely disappeared, and in others it was reduced to a thin fibrous strand. The choroidal blood vessels showed extreme thickening of their walls and almost complete obliteration of the lumens. The rod and cone fibers of the retina and their nuclei exhibited secondary atrophy. The inner retinal layers were normal. The retinal pigment epithelium had completely disappeared except for a small amount in the macular region. The findings in these eyes confirm the early postulate that the ophthalmoscopic changes in choroideremia are brought about by disappearance of the choroid. The changes in these specimens suggest that the disappearance of the choroid is due to a progressive obliteration of the choroidal arteries. Herson and Sampson[79] found that the development of vascular changes in the choroid and retina in essential polyangiitis (polyarteritis nodosa) is of grave import, for the four patients they observed survived only six weeks after discovery of the first ocular signs. In three of these patients nodules of choroiditis were noted, which rapidly regressed to the formation of pigmented scars.

## NEOPLASMS

The nature and origin of malignant melanomas of the uveal tract continue to cause much speculation, with little proof as to their origin. Moro[80] observed unmyelinated nerve fibers in melanomas; these fibers had no demonstrable con-

75. Meves, H.: Elastic Tissue in the Vessels of the Eye, Arch. f. Ophth. **149**:275-281, 1949.

76. Loewenstein, A.: Glomus Cells in the Human Choroid as the Basis of the Arteriovenous Anastomoses, Am. J. Ophth. **32**:1651-1659, 1949.

77. Pagliarani, N.: Pathological Changes in an Eye of a Newborn with Icterus Gravis Due to Isoimmunization by the Rh Factor, Boll. d'ocul. **28**:625-32, 1949.

78. McCulloch, J. C.: Pathologic Findings in Two Cases of Choroideremia, Tr. Am. Acad. Ophth. **54**:565-572, 1950.

79. Herson, R. N., and Sampson, R.: Ocular Manifestations of Polyarteritis Nodosa, Quart. J. Med. **18**:123-132, 1949.

80. Moro, F.: Morphobiology of Melanomas of the Choroid: I. Presence of Nerve Fibers in the Intraocular Neoplastic Mass, Ann. ottal. e clin. ocul. **75**:239-252, 1949.

nection with either the tumor cells or the blood vessels. This finding does not prove that the cells of the tumor arise from the sheaths of the nerve fibers, nor does the author so indicate.

Wolff [81] presents arguments against the neurogenic origin of the melanoma, indicating that if the cells of the neoplasm arise from the sheath of Schwann it should be a benign tumor.

Loewenstein [82] points out the production of mucus in the cells forming the walls of the cysts in cystic nevi, an indication of their epithelial origin. He investigated two choroidal nevi by means of flat and transverse sections and observed melanophores and melanoblasts, noting the resemblance of these cells to those of a neurofibroma. He indicates that the mesodermal structure of a melanoma does not exclude its origin from retinal pigment epithelium because outgrowths from this layer may show a typical mesodermal character.

Wright [83] studied 222 cases of malignant melanoma, of which 86 were uveal melanomas. The follow-up observation covered a period of 23 years. Of the patients with ocular tumors, 62.5 per cent survived five years and 39.4 per cent 10 years. Larger tumors, heavy pigmentation, diffuse growth and melanomas appearing in older age groups carried a poorer prognosis. The prognosis for more deeply pigmented tumors was poorer than that for melanomas of the epithelioid type. If there was extraocular extension, the average survival was less than two years. There was orbital recurrence in 8.3 per cent of the cases with an average survival period of four months.

Two cases are reported in which death occurred 30 and 36 years after removal of a probable primary ocular malignant melanoma,[84] and in another case a melanoma metastasized to the opposite orbit three years after enucleation of the original eye.[85] Another unusual case [86] was reported in which one eye was enucleated for a malignant melanoma. Several months later roentgenographic evidence of metastasis appeared in the sacroiliac region, and a melanoma was also discovered in the opposite eye and in the middle meatus of the nose on the same side. It is not possible to prove whether this case was an instance of bilateral primary melanoma or of metastasis from one eye to the other.

One instance of leiomyoma of the ciliary body is reported [87] and one of the iris.[88]

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Wadsworth [89] adopts Nordmann's classification of epithelial tumors of the ciliary body: I. Benign: (*a*) hyperplasia and (*b*) benign epithelioma (adenoma); II. Malignant: (*a*) embryonic (dictyoma) and (*b*) adult type. He states that the apparently high percentage of inflammation as a cause of benign epithelioma is interesting but not significant, because 41 per cent of 1,938 consecutive eyes enucleated at the Institute of Ophthalmology in New York either showed pathological evidence or had a history of inflammation. These benign epitheliomas showed very little or a low incidence of inflammation.

The method of formation of so-called benign adenomas is described as a primary invasion of the pigment epithelium into the adjacent stroma a short distance, followed by hyperplasia of the unpigmented epithelium within the invaginated pigment layer and, finally, a breaking through of unpigmented cells into the stroma of the ciliary body.

Greear [90] cites Godtfredsen's paper on metastatic carcinoma of the eye. He found that carcinoma was one-third to one-half as frequent as melanoma and that carcinomas of the lung metastasize as frequently as do those of the breast (carcinomas of the breast are 10 times as prevalent, however). The choroid temporal to the disk is the site most frequently affected. At times metastases are multiple and may lodge in the iris and ciliary body, as well as the choroid, or may be multiple in the choroid. The usual survival period after observable metastasis to the eye is six months to a year. It is suggested that roentgen and conservative treatment be carried out in cases of this lesion.

Two cases of metastasis of a testicular chorionic epithelioma to the choroid are reported,[91] making a total of five cases of this tumor in males now reported in the literature.

A nevoxanthoendothelioma of the iris was found in the enucleated eye of a Negro male infant, who presented inflammation of the eye, infiltration of the iris and ciliary body, dislocation of the lens and secondary glaucoma.[92] Shortly after enucleation the cutaneous lesions of this condition appeared, and excision and microscopic study of a specimen showed the lesion to be a nevoxanthoendothelioma. The cells in the iris resembled those of the tumor in the skin, and the infiltration of the iris was diffuse and dense and contained giant cells of the Touton type. Nevoxanthoendotheliomas of the skin may occur as red to yellow growths; they are present at birth or appear during early childhood. They tend to regress spontaneously over a period of years. It is believed that these tumors represent a nevus which is formed by overgrowth of embryonic mesenchymal cells or endothelial cells and that the xanthoma-like condition results from fatty changes in the cells during their dissolution.[93]

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# Correspondence

## MALIGNANT MELANOMA OF THE UVEAL TRACT

*To the Editor:*—With reference to the article by Dr. William E. B. Hall entitled, "Malignant Melanoma of the Uveal Tract: Report of Case with Death Thirty Years After Enucleation," published in the September 1950 issue of the ARCHIVES, page 381, I am far from convinced that this report has a reasonable relation to its title.

The author has arrived at the conclusion from autopsy findings only, coupled with the hearsay history, resurrected 30 years after an injury to the left eye and 40 years after an injury to the right leg, that a melanosarcoma existed in an eye which he had never seen. He assumes that the postmortem condition was the end result of an ocular sarcoma which was diagnosed as such without histological proof by the surgeon who removed the eye 30 years before.

I do not think it proper that the readers of the ARCHIVES should accept without challenge the conclusions tabulated in connection with this report.

1. There is no medical record of a hospital or physician indicating that there was a tumor in the left eye, which was removed. The author fails to take into consideration the history obtained by the intern that the patient had sustained an injury to the left leg 40 years before and that he remembered being in the hospital 13 years ago.

2. The author feels that if an exenteration of the orbit had been performed metastases and death would not have occurred. He states:

> The size of the initial lesion is insignificant, the original melanoma in this case occurring as a persisting recurrence or extension within the collapsed folds of Tenon's capsule.

In my experience melanosarcoma of the orbit extending to the optic nerve causes death by extension to the brain, and not by metastases to the liver. Metastases to other parts of the body, in my experience, usually occur after enucleation and are the result of travel of dislodged cells through the blood stream to the lungs, liver, vertebrae and other organs.

3. The author states that Tenon's capsule is a protective membrane in controlling an extension of the tumor. I do not feel that this proves anything. That trauma serves as an etiological factor in melanosarcoma, I heartily agree; but in this case it might have been an injury to the thigh 40 years ago. I cannot interpret this statement by the author:

> . . . . The initial complication of glaucoma, rupture of the eyeball and probably necrosis of the initial neoplasm may have been factors in the remarkable delay in this case.

There is no medical evidence from the history that the patient did have glaucoma, that he had rupture of the eyeball or that a neoplasm was present in the eyeball. This is purely an assumption based on a vague history obtained from the widow, 30 years after the alleged injury to the eye.

4. The author states:

> Death in this case came as a result of a non-neoplastic embolism arising from within the inferior vena cava, produced solely by a vascular pressure effect of a metastasis to the liver.

In a previous paragraph of the report it is noted that an operation was performed for a compression lesion of the spine of the first lumbar vertebra.

> After the operation the patient in his fixation cast complained of pressure on the chest, oppression and shortness of breath and frequently attempted to get up. About twenty-four hours after his operation, after an attempt to get propped up in bed, he suddenly began to choke. Collapse immediately followed, and death occurred in several minutes. . . .

It was felt that the postoperative immobilization of the patient in his cast, the pressure effect of the cast on the liver and the pressure of the enlarged liver and its major metastatic nodule on the subjacent vena cava resulted in a tremendous distention of the abdominal portion of the vena cava and the development of the thrombotic mass, which was suddenly swept away from its locus as a result of the patient's struggles and the subsequent propping up of his body, with actual elevation of the liver off the compressed vena cava.

Just what is meant by this statement is difficult to determine, but I conclude that the patient died 24 hours after the operation. Nothing in the history indicated that the patient was critically ill before the operation; there was no roentgenologic report, no blood study, not even a urinalysis. It is definite that the patient died and that autopsy showed melanosarcoma in the liver, in the lungs and in the eye socket.

It is again concluded that the original growth, presumably in the enucleated eye, had probably been less malignant than the tumor tissue in the metastatic organs.

It is difficult to pick up the loose ends in this confusing report, but the conclusions are out of tune with the observations. It would be more logical to say that 30 years after the injury to the eye the patient was found to have a melanosarcoma in the eye socket and lesions in the liver, lungs and other organs. It is quite possible for melanosarcoma to develop from nerve elements remaining in the orbital socket. It does not follow that because the patient had an injury 30 years before, the melanosarcoma existed at that time.

It is also quite possible that the patient had a lesion of the skin or other external part of the body and that all the findings at autopsy were secondary to an undiscovered original lesion.

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# News and Notes

EDITED BY DR. W. L. BENEDICT

## GENERAL NEWS

**Color Television of Ocular Surgery at Wills Eye Hospital.**—Medicine's superb new teaching aid, color television, was present at the third annual clinical conference of the staff and ex-residents of Wills Eye Hospital, on March 16 and 17, 1951, to bring assembled guests detailed close-ups of ocular surgery.

This was the first time that color television had been used for a specialists' meeting of any nature, although it was not the first time it had been used to depict eye surgery. In the 16 programs which the directors and sponsors, Smith, Kline & French, have produced at four other medical meetings, ocular surgery has frequently been presented.

"The medium lends itself particularly well to this application," Dr. I. S. Tassman, general chairman of the program for conference, explained, "the magnification afforded by color television provides details of operative technique which heretofore have not been afforded." This magnification of the eye on the television screen allows the audience to see a procedure even better than if they were at the scene of the operation.

The television program included several extracapsular and intracapsular cataract extractions to provide the audience with an opportunity to observe various technics in practice. The camera was set up in an operating room in the hospital, and the color signals were sent by coaxial cable to the main lobby of the hospital, where five special color receivers were set up.

The equipment, which Smith, Kline & French owns, and which they have been operating as a service to members of the medical profession since June 1949, was designed and built to their order for medical teaching purposes by the engineering research and development departments of the Columbia Broadcasting System.

## SOCIETY NEWS

**Georgia Society of Ophthalmology and Otolaryngology.**—The Georgia Society of Ophthalmology and Otolaryngology held its annual meeting at the General Oglethorpe Hotel, in Savannah, Ga., March 2 and 3, 1951.

The program was as follows: Cataracts as a Medical Problem and Selection of Type of Operation in Cataract Surgery, Dr. A. D. Ruedemann, Detroit; Diagnosis and Medical Treatment of the Glaucomas, and Surgical Treatment of the Glaucomas, Dr. Peter C. Kronfeld, Chicago; Surgical Treatment of Horizontal Muscle and of Vertical Muscle Deviations, Dr. William C. Owens, Baltimore; Functional Diseases of the Nose and Otolaryngological Mishaps, Dr. C. Stewart Nash, Rochester, N. Y.; Simple, Practical Therapeutic Measures in Otologic Practice—Surgical and Nonsurgical—and Conservation of Hearing in Chronic Suppurative Otitis Media, Dr. Philip Meltzer, Boston; Tumors of the Larynx—Benign and Malignant—and Summary of Otolaryngological Conditions that Require Expert Attention, Dr. Edwin C. Broyles, Baltimore.

## UNIVERSITY NEWS

**Wayne University Postgraduate Course in Basic Ophthalmology.**—Wayne University presents each year a postgraduate course in basic ophthalmology, beginning in September and is of nine months' duration. Classes meet from 8 a. m. to 5 p. m. on week days and from 8 a. m. to 12 m. on Saturdays. Mornings are spent in lectures and laboratories; afternoons, in the clinics of hospitals affiliated with the College of Medicine. Tuition for the course is $900, and the class is limited to 10 physicians.

Applications for the 1951-1952 class are now being accepted. Communications should be addressed to the Postgraduate Department at the College of Medicine, 1512 St. Antoine, Detroit 26.

# Book Reviews

**Researches in Binocular Vision.** By Kenneth N. Ogle. Price, $7.50. Pp. 345, with 182 illustrations. W. B. Saunders Company, W. Washington Sq., Philadelphia 5 and 7 Grape St., Shaftesbury Sq., London, W. C., 2, 1950.

As the title indicates, this volume is not a textbook of the physiology of binocular vision and spatial orientation. Its intent is not to cover the subject fully or to give a didactic presentation for beginners. Its aim is a detailed discussion of those aspects of binocular vision which have claimed the interest of the group of workers connected with the Dartmouth Eye Institute.

The book is divided into four parts. In the first part the methods of determining and evaluating the empirical longitudinal horopter are discussed. In the second part the fusional processes are considered. This section deals largely with the phenomena of sensory fusion; motor fusion is taken into account mainly in connection with the role of peripheral fusional stimuli in producing vertical fusional movements and in connection with a report of some investigations on cyclofusional movements.

The third and fourth parts of the book deal with aniseikonia in the broadest sense of the word. In the third part the changes are discussed which arise in binocular vision when a change occurs in the relative magnification of the images of the two eyes. The fourth part consists of an exposé of the experimental and theoretical basis of aniseikonia. The clinical aspects of the problem are not included.

The value of this book is twofold. The great amount of research work done at the Dartmouth Eye Institute—scattered in many publications—is brought within the covers of one book and within easy reach of any one. More important still, the detail work published in individual papers is placed within a broader perspective, and it becomes quite clear that all the work done at the Dartmouth Eye Institute contributes significantly to the support of the teachings of Hering and his school. The strict differentiation of objective (physical) and subjective (experiential) space, the appreciation of the stability of the retinal spatial values, and of the fact that spatial orientation has a sensory rather than motor basis, form the foundation of this teaching, which is relatively little recognized in the Anglo-Saxon literature. It is all the more to be welcomed that these points are so well elaborated throughout Ogle's book.

The book is very well got up; the print is excellent, and the figures (182 in number) are clear and well reproduced. A bibliography containing 259 references and a good index enhance the usefulness of this volume.

**Eye Surgery.** By H. B. Stallard, M.B.E., M.D., F.R.C.S. Second Edition. Price, $9.50. Pp. 667, with 550 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

In the second edition of this popular text on ophthalmic surgery, one finds many changes and additions, all of which portray the author's personal experiences. The introductory chapters remain essentially the same except for comments on the usefulness of fibrinogin and thrombin in skin grafting and on the value of amniotic membrane grafts in the treatment of second degree burns of the conjunctiva and cornea. The subject of reconstructive surgery is fully discussed, with more or less detailed descriptions of many recognized plastic procedures. This chapter, to which 178 pages are devoted, is probably the most valuable part of the volume, for in it, and in a later section on traumatic surgery, the surgeon's vast experience is fully

presented. To readers interested in these phases of ocular surgery these chapters will prove most helpful, for in them, with the aid of ample illustrations, are found concise descriptions of all types of reparative procedures. In the discussion on surgical treatment of lacrimal disorders mention is made of an operation called stricturotomy, in which a special instrument is used to divide the obstruction at the lower end of the lacrimal sac. Reformation of the stricture is prevented by repeated probings. To this reviewer the field of usefulness of this procedure appears limited. The standard operations on the extraocular muscles are adequately described, preference being given to the use of silk as a suture material. It is to be regretted that the term myomectomy, instead of myectomy, is still used to denote excision of a portion of the inferior oblique muscle. The subject of penetrating keratoplasty is presented in an orthodox manner, only minor variations in technics being given. The more recent thoughts on lamellar keratoplasty are also included in this discussion.

The usual intraocular operations are then described in sufficient detail to show clearly the author's exact technic, which differs but little from that of many others. While he correctly states that both intracapsular and extracapsular extractions have their field of usefulness, one infers from his long list of contraindications to removal of the lens in its capsule that the extracapsular method is the one he usually employs. In the discussion on complications of cataract extraction one is disappointed to find such brief mention of delayed reformation of the anterior chamber and secondary glaucoma. It is also surprising to this reviewer to see one advocating in selected cases couching of the lens—a procedure which in this country has long since been abandoned. In his summary on antiglaucoma operations he favors anterior flap sclerotomy with basal iridencleisis in cases of both acute congestive and chronic glaucoma and notes a trend away from iridectomy in the acute cases. This view is not shared by others, who still believe that iridectomy, if done early in the course of the acute attack, is the procedure of choice.

The surgery of retinal detachment is adequately presented, as is the use of electrocoagulation in hemangiogliomatosis retinae. The technic of radiotherapy for retinoblastoma is fully given, along with the results of its use in 24 patients. He also advocates this form of therapy for bilateral malignant melanoma of the choroid and states that in the future it may be the treatment of choice for unilateral growths seen in the early stages.

This volume is clearly printed, well illustrated and concisely written. It gives the technic of an experienced surgeon; so much can be learned from it.

**La Vision nocturne et ses troubles.** By Gaëtan E. Jayle and Albert G. Ourgaud, with the collaboration of P. H. Benoit, G. Blet and P.-V. Bérard. Report presented to the Société française d'ophtalmologie on July 26, 1950. Pp. VIII plus 863, with 455 figures. Masson & Cie, 120 Boulevard Saint-Germain, Paris,[6e] 1950.

The custom of the French Ophthalmological Society to publish an extensive report on a specific phase of ophthalmology, submitted by one or more of its members, has resulted in a series of outstanding monographs, some of which have become classics in the field. The present report is no exception. It is without a doubt the most comprehensive and up-to-date review of the physiology and pathology of night vision, a subject which has received a tremendous amount of attention during the last 15 years, and especially during the late war.

Faced with so huge a tome, a reviewer can only hope to give a general idea of the wealth of material which it contains.

The physiology of photopic and scotopic vision is discussed adequately in the first chapter, by P. B. Benoit. The normal dark adaptation curve and its variations under the influence of different experimental conditions received detailed attention in the second chapter. This chapter is of practical importance for all those who expect to engage in experimentation on the subject.

The next chapter deals with the general characteristics and variations of night vision in the normal person. All aspects of night vision are taken into consideration, including the behavior of the visual fields under conditions of night vision, the differential threshold, visual acuity, the sensation of movement, night myopia, stereopsis and flicker. Physiological variations of night vision, as well as the influence of anoxia on the light sense, are treated in the same chapter, while a separate chapter is devoted to the influence of drugs and toxic substances on the night vision of normal persons.

In the fifth chapter the optimum conditions for the study of night vision and the question of the possible improvement of night vision by physical or chemical means are examined. Practical conclusions drawn from this chapter are presented in the following chapter by G. Blet. Blet has also contributed the chapter on adaptometry, which includes an introduction on the units used and the basic principles of photometry. A very detailed account of all instruments in use for adaptometry follows in this chapter and should be extremely helpful, since it brings together in relatively small space a wealth of information on the various methods devised for the study of the absolute threshold, the differential sense, the morphoscopic sense, etc.

A special chapter is reserved for the technic employed by the authors in their own investigations. These investigations are discussed in the following two chapters, which represent the second half of the book. These two chapters bring together in great detail what is known about the behavior of dark adaptation under pathological conditions. Chapter nine is concerned with general pathological conditions—nutritional deficiencies; pathological conditions connected with pregnancy; diseases of the liver, the thyroid, the digestive tract and the skin; pulmonary tuberculosis; diseases of the kidneys, and the circulatory system; malaria; diabetes, and diseases of the central nervous system. The tenth chapter, the most interesting one to the ophthalmologist, deals with ocular diseases and their relation to dark adaptation. A good deal of space is given to the behavior of dark adaptation in glaucoma. Not only is the literature extensively cited, but the authors also present a series of personal observations. They conclude that in primary glaucoma the dark adaptation curves are decidedly more abnormal than those in secondary glaucoma. They believe that the dark adaptation curves may constitute an early symptom of great diagnostic value in primary glaucoma. Considerable space is also reserved for retinitis pigmentosa and hereditary, as well as acquired, degenerative diseases of the retina and choroid. Sections on the behavior of the dark adaptation curve in cases of retinal detachment, disturbances of the refractive media, disturbances of color vision and disturbances of the optic nerve and optic pathways occupy the rest of the chapter.

The greatest value of this book, in addition to the personal observations reported by the authors, lies in the thoroughness and care with which the literature from the earliest days to the latest publications (1950) is covered. It is gratifying to note the truly international scope of this survey of the literature. The bibliography occupies 81 pages. It is, nevertheless, the one feature of the volume which did not fully satisfy the reviewer. Instead of appending the references to each chapter or collecting the whole bibliography at the end of the volume, numbering it currently and referring to it in the text, the authors sum up the bibliography at the end of the volume and divide it into four chapters, under the headings of physiology, technics, general pathology and ocular pathology. Since many physiological or technical papers are necessarily cited in the pathological section and vice versa, one is sometimes at a loss as to where to find a given paper and has to look for it in more than one section. Also, it is unfortunate that many papers which are cited in the text extensively cannot be found in the bibliography. Furthermore, since within the text the reference to an author's work is by means of the year in which the paper was published, and since there is no further distinguishing mark, it is often difficult in the case of authors who have published a number of papers in the same year to determine in which of these papers the particular reference

can be found. Finally, in spite of the amazing excellence with which the literature is covered, there are an undue amount of typographic errors, and considerable inconsistency in the spelling of the names of other than French authors. The lack of an index may be found regrettable by some, but it is not as noticeable as one would expect in a book of this size, since the table of contents is extremely detailed.

These complaints may seem specious in view of the tremendous work which the authors have obviously put into this volume. The criticism should not be interpreted as a sign of ingratitude toward the authors, who have given us so much. Without any question, this volume will remain for a long time to come the most valuable survey of the whole field of night vision and its disturbances, and it will undoubtedly be studied often and with profit by all those who are interested in this field. The authors of the book, and the French Ophthalmological Society, deserve our congratulations and a vote of thanks for their splendid achievement.

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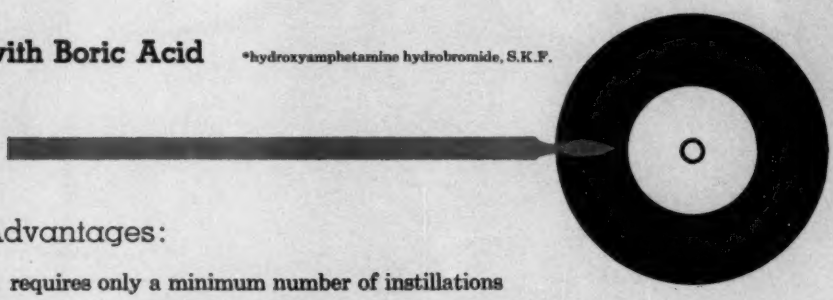

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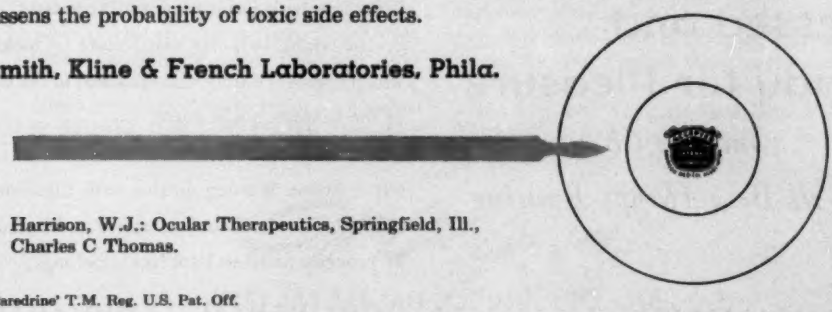

1. Harrison, W.J.: Ocular Therapeutics, Springfield, Ill., Charles C Thomas.

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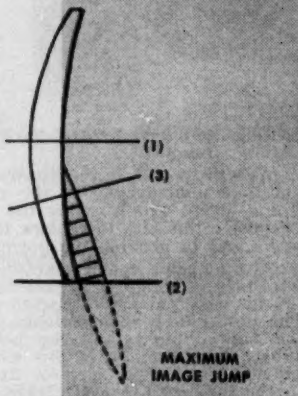
Three optical centers of concern in bifocals are illustrated in the diagrams. They are:

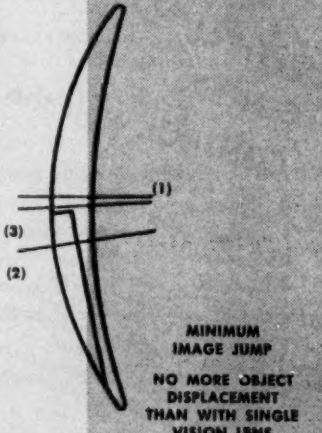
(1) The distance optical center
(2) The optical center of the segment only
(3) The resultant optical center of the combination of distance portion and segment.

The placement of (1) and (2) relative to each other controls the position of (3). Each standard segment shape has its optical center in a definite place. The positions of (2) and (3) control two important bifocal characteristics: image jump (more properly termed differential displacement) and object displacement. Image jump is a result of (2) not being on the segment's top border. Object displacement results when (3) is not at the reading level of the segment.

It is not possible to eliminate image jump and object displacement simultaneously. It is generally recognized that image jump (and co-incidental effects) is the more important factor. Modern segment shapes (flat or near-flat top types) introduce a minimum of image jump while object displacement is the same as in single vision lenses of equivalent power. It is significant that wearers of flat (or near-flat) top segments are rarely conscious of object displacement, hence this factor seldom need be considered.

Very few bifocal prescriptions permit elimination of object displacement with standard segments. When object displacement is reduced or eliminated, image jump is increased and the other advantages of the modern segment types necessary for image jump elimination are lost.

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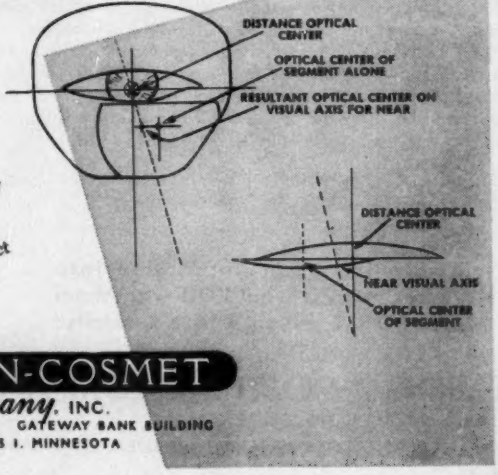
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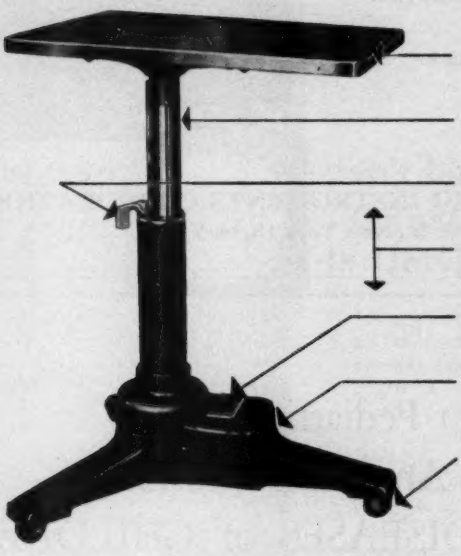

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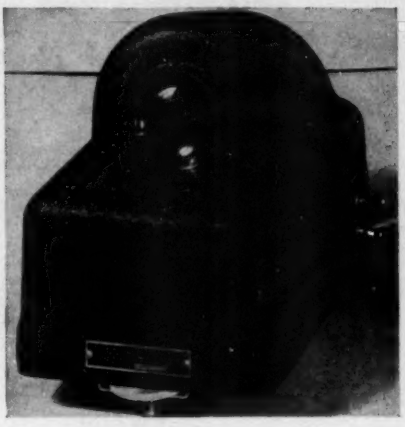

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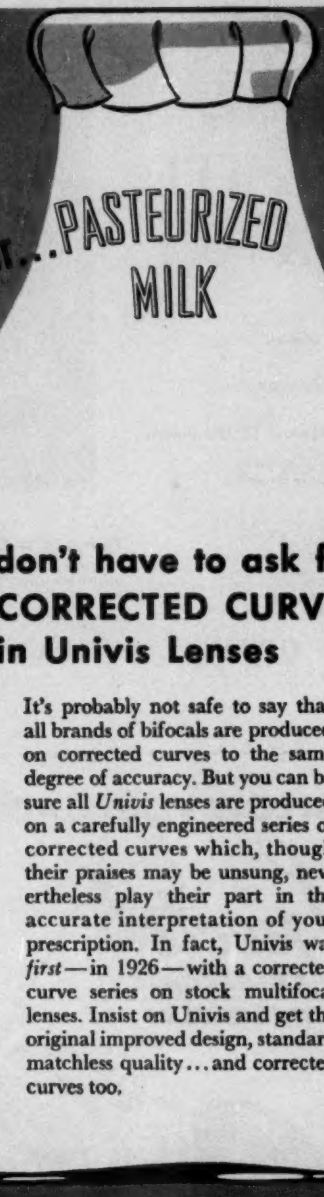


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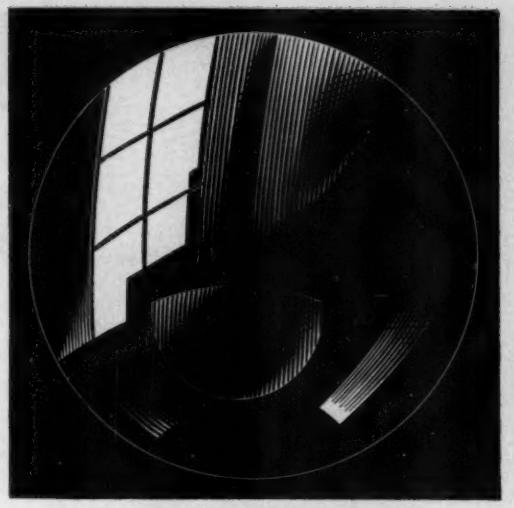

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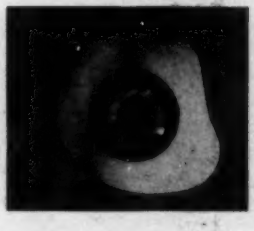

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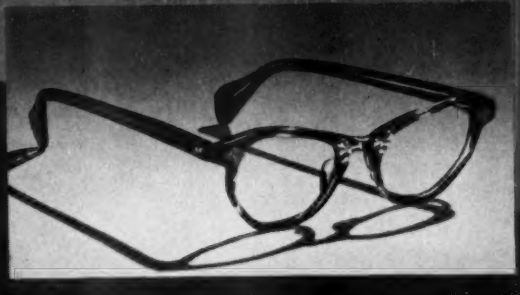

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